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## Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management

Daniel Caplivski and W. Michael Scheld

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# A College Student with Altered Mental Status

**Chapter:** A College Student with Altered Mental Status
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 21-year-old male college student presented with the sudden onset of fever and confusion. He initially had complained of a mild headache and nausea, but six hours later his roommates found him to be non-coherent and agitated. In the emergency department, the patient was febrile and hypotensive with nuchal rigidity. He was noncommunicative and lethargic, and was intubated for airway protection. Blood cultures were drawn immediately, and vancomycin and ceftriaxone were initiated. Cerebrospinal fluid analysis was notable for numerous white cells (20,894 WBC/μl, 71% neutrophils 25% bands), hypoglycorrhachia (glucose ⟨ 1 mg/dl), normal protein (41 mg/dl), and intracellular Gram-negative diplococci on Gram stain (Figure **1a.1**).

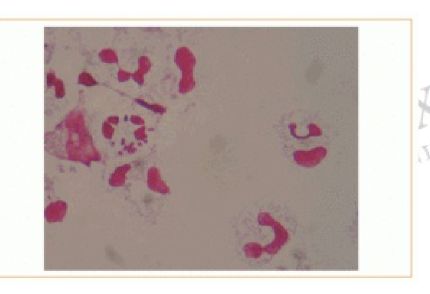





Figure 1a.1.
Gram stain of cerebrospinal fluid showing intracellular Gram-negative diplococci.

The patient's hypotension responded to an intravenous fluid resuscitation, and he did not require vasopressors. Within 48 hours the patient was extubated, alert, and felt back to his normal state of health. He never developed a rash, denied further headache, and recovered without focal neurologic deficits. Blood cultures eventually grew *Neisseria meningitidis* serogroup Y, and the patient completed a 14-day course of intravenous ceftriaxone. Two years prior to admission, the patient had received the nonconjugate polysaccharide meningococcal vaccine after a diagnosis of non-typeable *N. meningitidis* left knee septic arthritis. Evaluation during that hospitalization revealed a total complement (CH50) of 8 units/mL (normal range 101–300 U/mL), a C7 complement level of 6 U/mL (normal range of 36–60 U/mL) and normal C3, C4, C6 and C8 levels.

#### Case 1a Discussion: *Neisseria meningitidis* Meninigitis

Each year, an estimated 1,400–2,800 cases of meningococcal disease occur in the United States, a rate of 0.5–1.1/100,000 population.[1] *N. meningitidis* colonizes mucosal surfaces of the nasopharynx of humans, and is transmitted through direct contact with large-droplet respiratory secretions from patients or asymptomatic carriers. The case–fatality ratio for meningococcal disease is 10%–14% in the United States, despite little drug resistance and access to effective antibacterials and supportive care.[1] Patients who survive often have serious neurologic sequelae or loss of limbs. During 1991–2002, the highest rate of meningococcal disease (9.2/100,000) occurred among infants aged ⟨1 year; the rate for persons aged 11–19 years (1.2/100,000) also was higher than that for the general population. The rate in college students is similar to age-matched persons in the general population; however, living in a dormitory increases the risk for college students compared to students living off campus.[1]

In the United States, more than 98% of cases of meningococcal disease are sporadic, but there may be a trend toward more outbreak cases.[1] Serogroups B, C, and Y are the major causes of meningococcal disease in the United States, each being responsible for approximately one-third of cases.[1] Serogroup B predominately affects infants, whereas 75% of patients 11 years of age and older have serogroup C, Y, or W-135.[1] This epidemiology is dynamic, and newer vaccines may have an impact on the incidence of nonvaccine types.

Disease in Complement-Deficient Patients

Patients with late complement (C5–9) deficiency are at substantially increased risk of invasive *N. meningitidis* infections (57% vs. 0.0072 % in normal hosts).[2] It has also been demonstrated that 5%–10% of individuals with invasive meningococcal disease have a complement deficiency, but this rate varies and is dependent on the extent of endemic meningococcal disease.[2] *N. meningitidis* is the most common pathogen in late complement-deficient patients and, unlike patients with early complement deficiencies, they are not at increased risk of *Haemophilus influenzae* or *Streptococcus pneumoniae* infections.[2] Compared to normal hosts, late complement-deficient individuals on average present later in life with meningococcal infections, and tend not to have as severe a course of disease.[2] This was seen in the rapid and full recovery of this patient, which is somewhat atypical for meningococcal meningitis. One study of 276 patients demonstrated 1.5% mortality in patients with a late complement deficiency and *N. meningitidis* infection, compared to 19% in the general population.[2] C7 complement deficiency tends to occur more frequently in Caucasians, although this patient was African-American.[2] As was demonstrated in this case, patients with late complement deficiencies are also at risk for developing recurrent meningococcal infections (41% recurrence rate vs. a 0.34% recurrence rate in normal individuals).[2]

## Vaccination Interval for Late Complement-Deficient (LCCD) Patients

The high risk and rate of recurrence of invasive *N. meningitidis* in LCCD individuals warrants vaccination against meningococcal disease in this group.[3] Until recently there was data available only for LCCD patients with the polysaccharide vaccine (serogroup A, C, Y and W-135). In a study from Russia, six new episodes of meningococcal infection developed in four patients in the group of 31 vaccinees (19%); six episodes in six patients developed in the same time frame, in the group of 14 nonvaccinated LCCD persons (42%).[4] Although there are no large studies of patients with late complement deficiency receiving the more recently developed conjugate vaccine (polysaccharide diphtheria toxoid conjugae, *Menactra*, Groups A, C, Y and W-135), serum bactericidal antibodies are higher when compared to the polysaccharide vaccine.[3] Based on expert opinion and the antibody response data, the Advisory Committee on Immunization Practices (ACIP) recommends conjugate vaccine in all patients with late complement deficiency.[1] The current recommendation in LCCD patients is revaccination with conjugate vaccine every five years.[3] There is no conclusive data regarding antibiotic prophylaxis in LCCD patients.

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## Television Intolerance

**Chapter:** Television Intolerance
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 35-year-old man with a history of asthma and glomerulonephritis with mild renal insufficiency presented with two days of sinus congestion and pain. He attended his office Christmas party, but left early because he developed a severe headache. That night he felt myalgias, rigors, fever to 101° Fahrenheit, and drenching sweats. By the next day he experienced nausea, vomiting, and photophobia, recalling that he found even the light of the television intolerable.

Upon initial examination in the emergency department he was alert and oriented, and his temperature was 37.9° Celsius, his heart rate 128 beats per minute, and his blood pressure 121/78. He had no neck stiffness or other meningeal signs and the initial evaluation focused on fever and vomiting, possibly from viral gastroenteritis. His laboratory values were remarkable for a leukocytosis of 11,300 WBC/μl and a creatinine of 2.1 mg/dl. Several hours into his evaluation he became increasingly confused, answering questions inappropriately and having visual hallucinations of caterpillars on the walls. On repeat physical examination, he was unable to touch his chin to his chest. Ceftriaxone, vancomycin, and dexamethasone were initiated, and a head CT scan and lumbar puncture were performed. Cerebrospinal fluid analysis revealed protein 424 mg/dl, glucose (20 mg/dl, and 370 WBC/μl (74% polymorphonuclear cells). Gram stain of the cerebrospinal fluid revealed sheets of lancet-shaped Gram positive diplococci (Figures **1b.1** and **1b.2**).

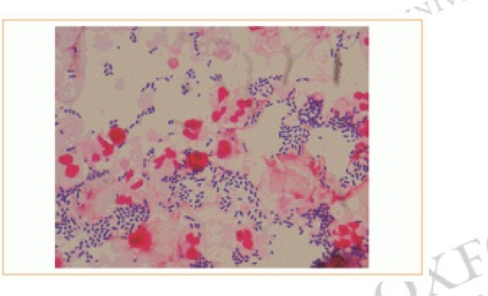


Figure 1b.1.
Gram stain of cerebrospinal fluid showing many white blood cells and innumerable Gram-positive cocci in pairs and chains. Many of the elongated forms had a classic lancet-shaped appearance.

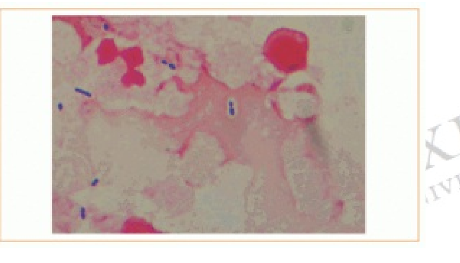




Figure 1b.2.
Gram stain of cerebrospinal fluid showing lancet-shaped diplococci and a clearing around one pair that highlights its polysaccharide capsule.

*Streptococcus pneumoniae* with a penicillin minimal inhibitory concentration of (0.03 µg/ml was recovered from the cerebrospinal fluid culture. The patient's mental status returned to normal with intravenous antibiotics and corticosteroids, but after several days of improvement his fevers recurred. A CT scan of the sinuses revealed a concha bullosa, nasal septal deviation, and a subtotal opacification of the left sphenoid sinus (Figures **1b.3** and **1b.4**). The patient underwent surgical removal of the concha bullosa, septoplasty, and debridement of the left sphenoid sinus, from which copious purulent material was released. Gram stain of this material revealed many polymorphonuclear cells, but no organisms were seen or recovered in culture. The patient's fevers resolved and he made a full recovery after treatment with intravenous ceftriaxone for 28 days. An immunologic evaluation did not reveal any acquired or inherited deficiencies.

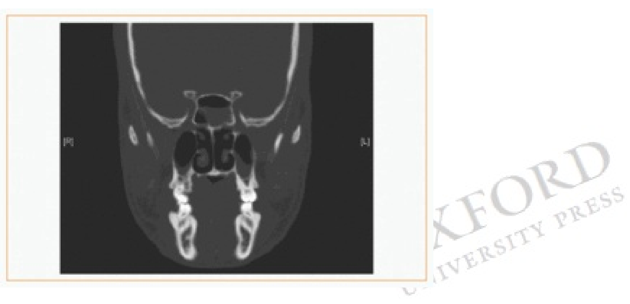


Figure 1b.3.
CT scan of the sinuses, coronal view revealed subtotal opacification of the left sphenoid sinus.

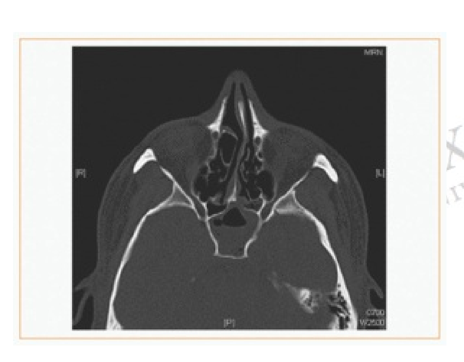




Figure 1b.4.
CT scan of the sinuses, axial view revealed a concha bullosa, nasal septal deviation, and a subtotal opacification of the left sphenoid sinus.

### Case 1b Discussion: *Streptococcus pneumoniae* Meningitis

## Clinical Features and Diagnosis

*Streptococcus pneumoniae* is one of the most common causes of bacterial meningitis in both adults and children worldwide. Also known as pneumococcus, it is a Gram-positive alpha-hemolytic Streptococcus, which can be identified in the laboratory by its susceptibility to Optochin, catalase negativity, as well as its lysis in bile salts. Although less commonly used in the clinical microbiology laboratory, the *Quellung* reaction highlights the bacterium's polysaccharide capsule by causing it to be more refractile and visible. Major virulence factors associated with *S. pneumoniae* include its antiphagocytic capsule, its capacity to adhere to pharyngeal cells, and its production of toxins such as pneumolysin, a specific factor resulting in neuronal loss in meningitis.[1]

Meningitis occurs when pneumococcal organisms invade the nasopharyngeal mucosa, cross the blood–brain barrier, and replicate in the cerebrospinal fluid (CSF). Because pneumococcus commonly colonizes the naropharynx, it is often encountered as the etiologic organism in sinusitis, otitis media, and pneumonia. Pneumococcal meningitis can occur via direct extension from a sinusitis, or from a basilar skull fracture causing a CSF leak. In the case described above, the concha bullosa (an air-filled nasal turbinate which may occlude the sinus ostia and cause recurrent sinusitis) likely played an important role in the persistence of the infection. Clinical features of pneumococcal meningitis include fever, headache, confusion, nuchal rigidity, and in severe cases, coma. The course of the disease is rapid, and mortality rates have been reported to be as high as 40%. Those at greatest risk for morbidity and mortality from invasive pneumococcal disease include asplenic patients, patients with complement deficiencies, and those with other acquired and congenital immunodeficiencies.[2]

Diagnosis is usually made by the identification of typical Gram positive lancet-shaped cocci in pairs on Gram stain of the CSF. An elevated protein, decreased glucose, and an elevated WBC count with a predominance of neutrophils in the CSF, all suggest bacterial meningitis. CSF and blood should be sent for culture and antimicrobial susceptibility testing, although, as in this case, blood cultures may be sterile despite positive CSF culture. Detection of pneumococcal antigens in CSF may aid in the diagnosis of pneumococcal disease in patients in whom antibiotics may inhibit recovery of the organisms in cultures; however, these assays have yet to show superiority over conventional Gram stain.[1]

## Treatment and Prevention

In 1990, few pneumococcal isolates in the United States showed high level ()2ug/ml) penicillin resistance, and only 5% showed moderate resistance, but rates of invasive disease due to penicillin-resistant pneumococci have been increasing. The current standard of care in treating pneumococcal meningitis before susceptibility testing is to use both a third-generation cephalosporin and high dose vancomycin intravenously. Selected third-generation cephalosporins, such as ceftriaxone and cefotaxime, are bactericidal agents with excellent CSF penetration. Vancomycin is not rapidly bactericidal, but penetrates the CSF adequately in the setting of meningeal inflammation. The antimicrobial regimen may be adjusted once susceptibilities are known. Surgical intervention may be required in cases of pneumococcal meningitis from anatomic problems, such as obstructive sinusitis or CSF leak.

Much of the pathogenesis of bacterial meningitis is linked to destructive effects of the intense inflammatory response of the immune system. Therapeutic interventions to lessen this damage have led to several trials of corticosteroids in bacterial meningitis, but this topic remains controversial. One large Scandinavian study showed that the early administration of dexamethasone in patients with pneumococcal meningitis decreased the overall mortality, as well as the rate of neurologic sequelae such as hearing loss.[3] Two other large studies in patients from Vietnam and Africa failed to replicate this benefit, though rates of tuberculosis and HIV in these populations may have played a role in the different outcomes.[4,5]

The heptavalent pneumococcal conjugate vaccine (PCV-7) and the 23-valent pneumococcal polysaccharide vaccine are the two vaccines effective against pneumococcus currently. PCV-7 contains the 7 capsular polysaccharide antigens from the strains most commonly involved in pediatric infections; it is used in infants and children particularly, because the protein conjugation enables a more protective antibody response. The 23-valent polysaccharide vaccine provides protection against a much larger number of invasive pneumococcal serotypes, and is recommended for many categories of patients at risk for pneumococcal disease. These include adults over 65, patients with chronic pulmonary disease, and patients with immunocompromising conditions such as HIV infection, diabetes, asplenia, and chronic renal insufficiency. Repeat vaccination at 5–7 year intervals is recommended for maintenance of protective immunity.[6]

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## Gait Instability and Slurred Speech in an Immunosuppressed Patient

**Chapter:** Gait Instability and Slurred Speech in an Immunosuppressed Patient
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 58-year-old man with a history of rheumatoid arthritis and myasthenia gravis presented with a 2-week history of fever, nausea, vomiting, and diarrhea. He also had an acute onset of slurred speech, worsening gait instability, inability to stand, confusion, and loss of bowel and bladder function. His immunosuppressive medications included azathioprine 50mg/day and prednisone 40 mg/day.

On presentation the patient was febrile (102.9° Fahrenheit) and unarousable, but moved all extremities in response to painful stimuli. He has scattered 2–3mm maculopapular, nonblanching lesions from his bilateral knees to the dorsum of his feet (sparing the soles) and on the bilateral elbows (Figure **1c.1**).





Figure 1c.1.
The rash on the lower extremities consisted of 2–3mm maculopapular, non-blanching lesions from his bilateral knees to the dorsum of his feet (sparing the soles).

Due to his altered consciousness, signs of meningeal irritation could not be reliably assessed, and he was intubated for airway protection.

Laboratory values were significant for hyponatremia (130 mmol/L), but were otherwise unremarkable. Lumbar puncture (LP) revealed an opening pressure of 380 mm Hg, 72 RBC/µl, 36 WBC per µl (41% neutrophils, 37% lymphocytes, 21% monocytes, 1% eosinophils), protein 50 g/dl, and glucose 18 mg/dl. Gram stain revealed numerous polymorphonuclear cells, no bacteria, and budding yeast cells (Figure **1c.2**). A CSF cryptococcal antigen titer was greater than 1:2048. CT scan revealed numerous acute cerebral infarcts, and brain MRI confirmed leptomeningeal enhancement, along with numerous bihemispheric acute infarcts involving the grey and white matter (Figure **1c.3** and **1c.4**).

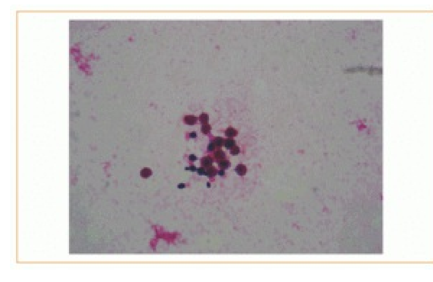




Figure 1c.2.
Gram stain of the cerebrospinal fluid showing numerous polymorphonuclear cells and budding yeast cells (original magnification 100x).

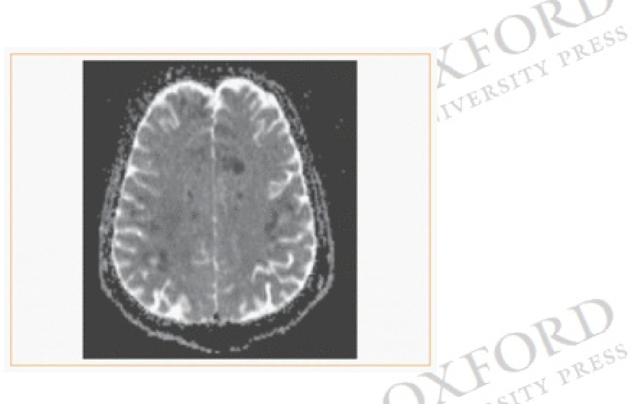




Figure 1c.3.
CT scan brain, axial view showing numerous acute cerebral infarcts.

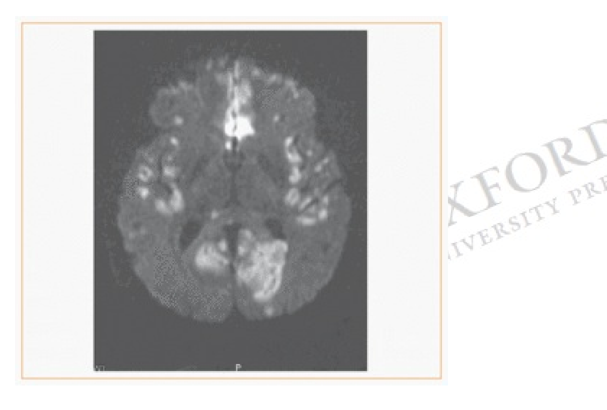




Figure 1c.4.
Brain MRI, axial view showing leptomeningeal enhancement as well as numerous bihemispheric acute infarcts involving the grey and white matter.

Blood and CSF cultures were positive for *Cryptococcus neoformans,* and the patient was treated with liposomal amphotericin and every-other-day lumbar punctures. Because of persistently positive CSF fungal cultures, high dose fluconazole (800mg/d) was added for induction therapy. The patient's opening pressure eventually decreased to less than 250 mm Hg, CSF cultures were sterilized, and he was continued on oral fluconazole. The patient's clinical status improved, but he was left with chronic neurologic sequelae.

**Case 1c Discussion: *Cryptococcus neoformans* Meningitis**

*Cryptococcus neoformans*, which causes the vast majority of human cryptococcal infections, has evolved into three distinct varieties (*var gattii, grubii,* and *neoformans*). *C. neoformans var neoformans* is the most common causative pathogen in both immuno-competent and immunocompromised hosts.[1] While *Cryptococcus* accounts for 45% of meningoencephalitis cases in AIDS patients in sub-Saharan Africa, it is a rare cause of CNS disease in HIV-negative patients. In the pre-AIDS era, it was estimated that there was an overall incidence of 0.2–0.8 cases per 100,000 person years in the United States.[1] The development of aggressive surgeries, organ transplantation, and immunosuppressive therapies has led to an increase in the overall prevalence of invasive fungal diseases, including cryptococcosis, in HIV-negative individuals. Additionally, some reports indicate immunocompetent patients with cryptococcosis may have increased mortality and chronic neurological sequelae as compared to immunocompromised patients. The worse prognosis in this group is hypothesized to be secondary to a more inflammatory immune response, as well as delay in recognition.[2]

## Clinical Features of CNS Cryptococcosis

The most common sites of cryptococcal infection include the lungs (the most common portal to infection), followed by the central nervous system and the skin. Clinical manifestations and site of infection are determined by the level of immunosuppression and by the infecting variety. A study by Mitchell and colleagues indicated that *C. neoformans var gatii* was more likely than *C. neoformans var neoformans* to cause disease in immunocompetent hosts. Patients infected with *gatii* varieties tended to have more invasive parenchymal disease, cryptococcomas, and hydrocephalus.[2] Immunosuppressed patients may also manifest an immune reconstitution syndrome, leading to worse clinical symptoms despite having negative cultures and antigen assays. This phenomenon is seen when antiretroviral therapy leads to a recovery of cell mediated immunity, or when immunosuppressive medication effects wane.[1]

Patients with CNS cryptococcosis may present with symptoms of acute, subacute, or chronic meningitis or meningoencephalitis, including headaches, fever, cranial nerve abnormalities, altered mental status, memory loss, or coma.[1–3] A presenting semicomatose state in both immunocompetent and immunosuppressed patients has been shown to be a poor prognostic factor.[3] Studies in immunocompetent patients indicate that presenting symptoms are often chronic, and include headaches, weakness, and fevers.[2,3] They are less likely to present with extraneural cryptococcosis (pulmonary, cryptococcemia, cutaneous) as compared to immunocompromised individuals. Immunocompetent hosts are more likely to present with parenchymal disease, higher levels of CSF inflammatory cells and protein, but lower levels of cryptococcal antigen.[1]

A lumbar puncture (LP) is indicated in all patients suspected of CNS disease and all immunosuppressed patients with pulmonary disease or cryptococcemia. Lumbar puncture should be performed in the lateral decubitus position, and evaluated for opening pressure, protein, glucose, cell profile, and cryptococcal antigen with fungal culture. India ink stains, which detect yeast between $10^2$ and $10^4$ CFU/ml, are no longer routinely performed by many laboratories, but highlight the antiphagocytic polysaccharide capsule. CT scans of the head should be performed in immunocompromised patients suspected of cryptococcosis, to rule out space-occupying lesions. Patients will often demonstrate elevated opening pressure ()200 mm Hg), elevated protein, hypoglycorrhachia, and lymphocytic pleocytosis. In a study by Shih and colleagues, initial CSF antigen levels of greater than 1: 512 were an independent predictor of mortality.[3] Positive CSF cultures may be seen in patients in whom antigen is not detected (possibly due to acapsular invasive strains); therefore, culture is recommended even with a negative antigen test.

## Treatment

Prior to 1950, CNS infection with *Cryptococcus* was uniformly fatal, but with the advent of polyene antimicrobials such as amphotericin, treatment is successful 60%–70% of the time.[4] In 2000, the Infectious Disease Society of America (IDSA) published its CNS cryptococcosis treatment goals: to resolve infection through the use of antimicrobials, and to reduce long-term neurologic sequelae by controlling elevated intracranial pressure.[4] In HIV-negative patients, the guidelines recommend a 2-week induction course of amphotericin B (0.7–1 mg/kg/d) or liposomal amphotericin B (3–5 mg/kg/d) in those with renal impairment, plus flucytosine (100 mg/kg/d divided into 4 doses) for two weeks, followed by consolidation therapy with fluconazole (400mg/d) for a minimum of 10 weeks.[4] In immunocompromised HIV-negative patients, similar to HIV-positive patients, higher dose fluconazole consolidation therapy (400–800 mg/d) may be used followed by 6–12 months of suppressive fluconazole (200mg/d).[4] Additional therapies include an extended combination of amphotericin B plus flucytosine for 6–10 weeks.[4] Therapies studied in HIV-positive patients that have not yet been validated in HIV-negative patients include induction amphotericin with high dose fluconazole (800mg/kg/d) followed by consolidation fluconazole therapy.[5]

Elevated cranial pressures can be seen in up to 50% of non-HIV-infected patients and, therefore, follow-up lumbar punctures are an important adjunctive therapy to monitor infection and relieve elevated intracranial pressure. The goal pressure is ≤200 mm Hg or 50% of the initial opening pressure.[5] Lumbar punctures with culture should be performed daily until the pressures have normalized, but lumbar drains or ventriculoperitoneal shunts may be necessary for patients with refractory disease. In patients who have normal initial opening pressure, subsequent lumbar puncture with culture should be performed after 2 weeks to confirm CSF sterilization. Patients with nonclearing cryptococcomas may require surgical excision.[1]

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## A 38-year-old Woman from Thailand with Pulmonary Infiltrates and Meningitis

**Chapter:** A 38-year-old Woman from Thailand with Pulmonary Infiltrates and Meningitis
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### Case Presentation

A 38-year-old woman from Thailand, who had immigrated to the United States 10 years prior to presentation, was admitted with several days of fever, headache, nausea, and vomiting. Three days prior to admission, she also developed confusion. On physical examination she was very cachectic, confused, febrile (temperature 38.8° Celsius), and tachycardic (heart rate 111 beats per minute). Her pulmonary exam was significant for crackles in the upper fields bilaterally, but the rest of the physical examination was unremarkable.

Laboratory examinations were notable for peripheral leukocytosis (13.5 × $10^3$ WBC/μl, 79.4% neutrophils, 13.4% monocytes), anemia (Hgb of 11.5gm/dl), and hyponatremia (sodium 125 meq/l). Head CT showed no mass-occupying lesions, and lumbar puncture revealed 1010 WBC/μl (63% neutrophils, 10% monocytes, and 27% lymphocytes), elevated protein (340mg/dL), 3 RBCs/μl, and hypoglycorrhachia (glucose ⟨ 20 mg/dL). Gram stain, calcofluor white stain, and smears for acid fast bacilli on the cerebrospinal fluid were negative. Given the concern for bacterial meningitis, the patient was started on cefepime, vancomycin and ampicillin, with no clinical improvement. Her HIV test was positive and her CD4 count (44 cells/μl) and viral load (9,742 copies/ml) were consistent with advanced AIDS. Chest radiography showed bilateral upper lobe infiltrates (Figure **1d.1**) and neurologic imaging showed multiple infarcts of the thalami, cerebellum, frontal, and occipital lobes (Figures **1d.1** and **1d.2a**–**c**).

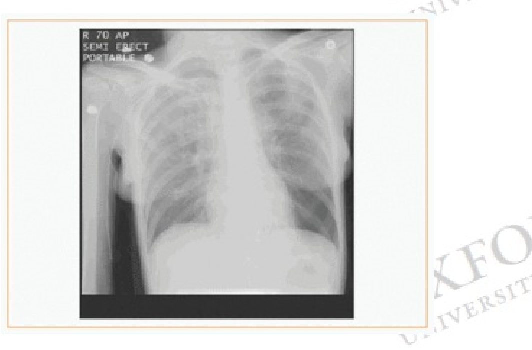





Figure 1d.1.
Portable anterior-posterior chest radiograph revealing bilateral interstitial infiltrates most prominent in the upper lobes.

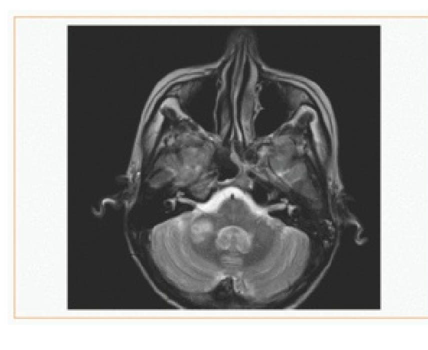




Figure 1d.2a.
Brain MRI, axial view, revealing cerebellar infarcts.

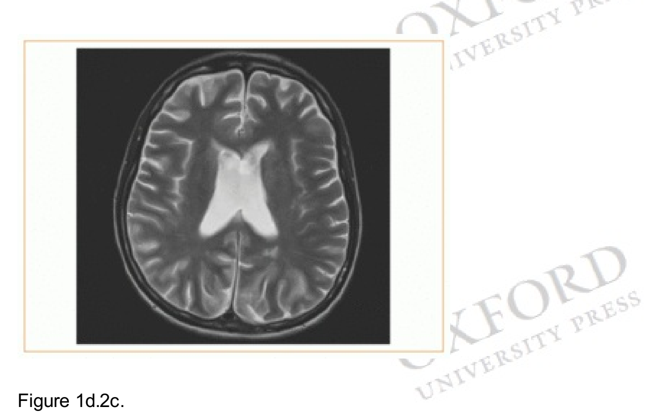




Figure 1d.2c.
Brain MRI, axial view, revealing frontal lobe infarcts.

Mycobacterium tuberculosis PCR on CSF was positive, and mycobacterial culture eventually grew *Mycobacterium tuberculosis*. Antibacterial antibiotics were discontinued, and isoniazid, rifampin, ethambutol, and pyrazinamide were initiated. Four days later, tenofovir, emtricitabine, and efavirenz were added, but the patient's worsening nausea, vomiting, and elevated liver enzymes prompted discontinuation of all medications. Liver function tests improved three days later, and isoniazid, rifampin, ethambutol, and pyrazinamide were restarted with the addition of moxifloxacin, given concern for resistant tuberculosis. One week later, with only mild improvement in the patient's neurologic status, susceptibility testing of the isolate first showed isoniazid resistance, so isoniazid was replaced with amikacin and cycloserine. Further testing revealed the isolate to be also resistant to rifampin, ethionamide, and streptomycin—but by the time full resistance testing was available, the patient's clinical status had declined and she died several days later.

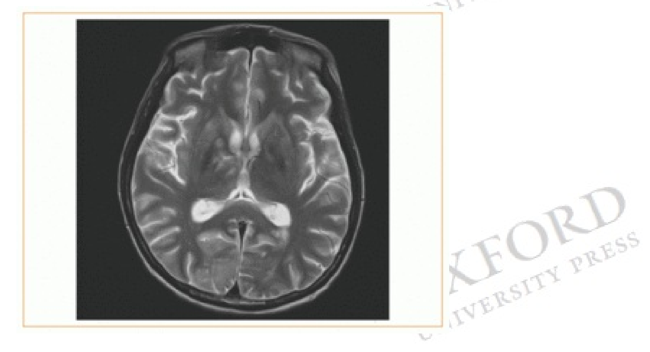




Figure 1d.2b.
Brain MRI, axial view, revealing occipital lobe infarcts.

**Case 1d Discussion: *Mycobacterium tuberculosis* Meningitis**

## Clinical Features and Diagnosis

The presentation of tuberculous meningitis mimics bacterial meningitis, with complaints of fever (68%–91%), headache (83%–100%), vomiting (77%–81%), nuchal rigidity, (68%–100%), and altered mental status (55%–72%), but the onset of symptoms is generally more subacute.[1] Other findings on physical examination may include cranial nerve abnormalities, such as facial nerve palsy (15%–45%). Depending on the symptoms, patients presenting with TB meningitis can be divided into Stage I – lucid with non-focal neurological signs or evidence of hydrocephalus; Stage II – lethargic, confused, with mild focal signs (cranial palsy or hemiparesis); or Stage III – with delirium, stupor, coma, seizures, multiple cranial nerve palsies, and/or dense hemiplegia.[1] Typical cerebrospinal fluid findings include opening pressure of 10–20cm $H_2O$, many white blood cells (100–500 cells/µl with lymphocytic predominance in 70%–90% of cases), elevated protein (100–500mg/dL), and hypoglycorrhachia (glucose ⟨ 45mg/dL). Acid fast bacilli smear is positive in CSF only 13%–20% of the time and only 10%–30% of cases are found to have positive CSF cultures. *Mycobacterium tuberculosis* PCR may be a useful adjunctive test, but its sensitivity and specificity is higher in smear-positive specimens. Chest radiography is abnormal in 50%–75% of cases with 9%–34% of patients presenting with a miliary pattern. Less than 50% of patients with tuberculous meningitis are PPD positive, but neurologic imaging may reveal hydrocephalus, basilar meningitis, focal brain lesions (tuberculoma), edema, or infarction, in 68%–94% of cases.[1]

## Treatment

Mortality due to TB meningitis is high, ranging from 19% (Stage I) to 65% (Stage III). A worse prognosis is associated with HIV infection and in patients presenting with CSF glucose ⟨ 40, protein ⟩ 1500mg/dL, and those who have other foci of TB besides the meninges.[1] Treatment of drug-susceptible TB includes 9–12 months of isoniazid, rifampin, pyrazinamide, and ethambutol (see Chapter 6 for full discussion).[2] Corticosteroids are often added to regimens for meningeal tuberculosis, particularly for patients presenting in more advanced stages of the disease.[3]

Treatment of MDR tuberculosis should be undertaken with the guidance of tuberculosis experts; a detailed discussion is beyond the scope of this book. As a general guideline, isolates resistant to isoniazid alone may be treated with rifampin, pyrazinamide, ethambutol, and a fluoroquinolone such as moxifloxacin for 6 months following a negative AFB smear. In patients with isoniazid and rifampin resistant TB, a fluoroquinolone, pyrazinamide, ethambutol, and an injectable agent (aminoglycosides like streptomycin, amikacin, or kanamycin), with or without another, second agent (cycloserine, clarithromycin, amoxicillin/clavulanate, ethionamide, p-aminosaliclyic acid), should be used for 18–24 months post a negative AFB smear.[4]

## TB and HIV Coinfection

In patients already taking antiretroviral medications, TB medications should be added to the antiretroviral regimen continued. In patients with CD4+ cell counts less than

100cells/μl, the benefits of treating both HIV and TB concurrently generally outweigh the associated problems of drug interactions, side effects, and possible inflammatory responses. Particular consideration should be given to interactions that arise from p450 inhibition by protease inhibitors. Both HIV and *Mycobacterium tuberculosis* exert a suppressive effect on the immune system, and treatment of either or both may lead to exacerbations of symptoms. In the case of HIV, the immune reconstitution inflammatory syndrome may require corticosteroids to lessen the inflammation. Similarly paradoxical reactions may be seen several weeks into treatment of tuberculosis. This worsening of symptoms may prompt concerns for resistant tuberculosis, but if cultures of repeat specimens are sterile, these exacerbations of symptoms may also be managed with corticosteroids.[2,5]

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## Fever and Confusion after Neurosurgery

**Chapter:** Fever and Confusion after Neurosurgery
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Clinical Presentation and History

A 63-year-old man with a history of hypertension, hyperlipidemia, and glaucoma was seen by a neurologist for progressive hearing loss in the left ear over the prior two years. He had also recently developed left-sided facial weakness and numbness, and MRI demonstrated a mass at the left cerebellopontine angle with extension into the left auditory canal, consistent with a vestibular schwannoma (Figure **1e.1**). The patient underwent left suboccipital craniectomy with tumor resection several days later, and he was discharged home after an uncomplicated postoperative course.

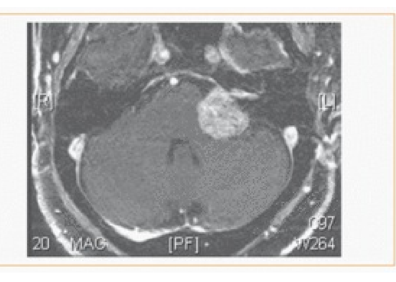





Figure 1e.1.
Brain MRI, axial view, demonstrating a mass at the left cerebellopontine angle with extension into the left auditory canal, consistent with a vestibular schwannoma.

Two days following discharge, the patient was readmitted with weakness, unsteady gait, and a headache. He was initially afebrile and answering questions slowly but appropriately, but on his second hospital day he was febrile (38.1° Celsius) and he became progressively confused. On physical examination, he had a left-sided facial droop, unchanged since surgery, and the incision on his scalp was clean with no exudate or erythema. He was lethargic, had difficulty following commands, and had nuchal rigidity. His speech was slow and slurred, but the rest of his physical examination was unremarkable.

Laboratory values were remarkable for leukocytosis (15.5 × $10^3$ WBC/µl) and thrombocytopenia (82 × $10^3$ platelets/µl). CT scan of the brain showed no hemorrhage, infarct, or mass, and CSF analysis revealed: 3540 white blood cells/µl (93% neutrophils); protein 112 mg/dl; glucose ( 20 mg/dl; and many Gram negative bacilli (Figure **1e.2**). The culture from the lumbar puncture grew heavy-growth *Klebsiella pneumoniae*, susceptible to ceftriaxone (Figure **1e.3**). The patient was initially treated with IV cefepime 2 grams every eight hours while awaiting culture results, and he eventually completed a 14-day course of intravenous ceftriaxone. His mental status returned to his baseline, and he was transferred to inpatient rehabilitation following completion of his antibiotics with no further complications.

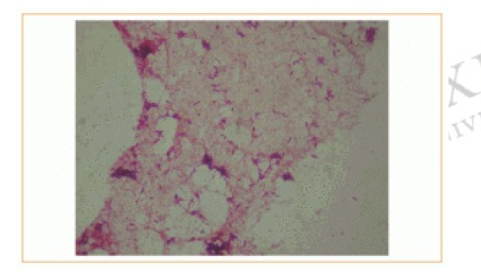




Figure 1e.2.

Gram stain of cerebrospinal fluid revealing numerous Gram-negative bacilli.





Figure 1e.3.
Cultures of cerebrospinal fluid culture on MacConkey agar and sheep's blood agar revealed a lactose fermenting organism with mucoid colonies.

**Case 1e Discussion: *Klebsiella pneumoniae* Meningitis**

## Clinical Presentation and Diagnosis

Spontaneous aerobic Gram-negative bacillary meningitis is relatively uncommon in the United States, contributing only a small proportion to community-acquired bacterial meningitis ((5%).[1] Most patients in whom aerobic Gram-negative bacillary meningitis develops spontaneously suffer from an underlying predisposing condition, such as alcoholism, liver cirrhosis, or diabetes.[1] Disseminated strongyloidiasis is a rare cause of meningitis with enteric pathogens, discussed in further detail in Chapter 9. Gram-negative bacillary CNS infections are more common, however, following neurosurgery or head trauma.[2] Diagnosis can be difficult in patients post-neurosurgery or head trauma, as they often cannot provide a history, and interpretation of CSF studies is complicated by postoperative inflammation.[2] Mortality in patients with Gram-negative bacillary meningitis is high (ranging from 15%–70%), as is the rate of postinfection neurologic sequelae.[1,2,3]

Retrospective reviews have demonstrated a range of neurosurgical procedures leading to the development of Gram-negative meningitis, including the insertion or revision of an external ventricular drain or shunt, excision or debulking of a tumor, aneurysm clipping, and repair of a CSF leak.[2] The risk of development of infection following a neurosurgical procedure is highly variable, ranging from ( 1% to 8%, with most series involving a limited number of patients. A recent review[4] of over 2000 patients who underwent a range of neurosurgical procedures demonstrated an incidence of postsurgical bacterial meningitis of only 0.3%, though other series[4] have found an incidence of 1.4%–1.9%.

Diagnosis of postsurgical bacterial meningitis is difficult, given the frequent development of noninfectious meningitis postsurgery, and the shared clinical presentation of chemical and bacterial meningitis. Most patients diagnosed with Gram-negative bacillary meningitis are febrile, with meningismus and altered mental status.[3] The diagnosis of bacterial meningitis is generally based on CSF studies; patients with bacterial meningitis usually have a markedly elevated CSF protein level, hypoglycorrhachia, elevated white blood cell count (with predominantly neutrophils) and, frequently, positive CSF Gram stain and culture.[2] Elevated lactate levels in the CSF have been shown to support the diagnosis of bacterial meningitis.[5]

The majority of Gram-negative bacilli isolated from the CSF are Enterobacteriaceae, particularly *Klebsiella pneumoniae* and *Escherichia coli*, but a range of other organisms have been recovered as well, including *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Acinetobacter haemolyticus*.[1] In addition to Gram-negative pathogens, *Staphylococcus aureus*, coagulase-negative Staphylococci, and *Propionibacterium acnes* are important considerations in postsurgical patients and those with shunts in place.[4]

## Treatment

Antibiotic choice must be based on both an understanding of the resistance patterns of nosocomial pathogens, as well as CSF penetration of antimicrobial therapy. The Infectious Disease Society of America Practice Guidelines recommend the use of vancomycin plus cefepime, ceftazidime, or meropenem in patients with meningitis post-neurosurgery, or with a shunt in place, while awaiting culture results.[5] Although aminoglycosides played a significant role historically, this class of drugs has poor CSF penetration and thus is generally inadequate when administered parenterally to treat Gram-negative bacillary meningitis. There is limited data to guide the use of antibiotic therapy intrathecally or intraventricularly; however, agents with poor CNS penetration are sometimes administered via this route to treat patients with very resistant bacterial pathogens.[5]

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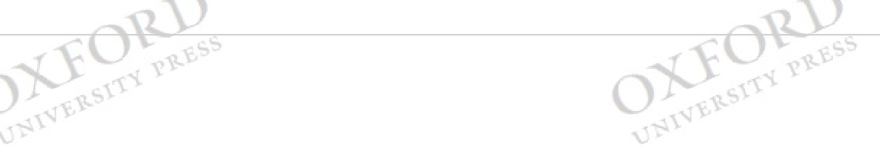






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## Recurrent Meningitis

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**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 69-year-old man, with a history of head trauma 10 years prior to admission, presented to the emergency department with a two-day history of headaches, photophobia, nausea, and vomiting. The pain was band-like, 10 out of 10, and not related to position. The patient also had a history of hypertension, hyperlipidemia, and coronary artery disease, and his medications included simvastatin, atenolol, lisinopril, and aspirin. He denied any other over-the-counter medications including nonsteroidal anti-inflammatory agents. He had had three prior episodes similar to this, in 1995, 2000, and 2004.

On physical examination, he had a mild fever (100.3° Fahrenheit), was difficult to arouse, and was not able to follow commands. He had meningismus and photophobia, but the remainder of his physical examination was unremarkable. CT and MRI of the head showed no evidence of masses, or temporal lobe or meningeal enhancement. Cerebrospinal fluid analysis revealed a lymphocytic pleocytosis (189 WBC/μl, 67% lymphocytes, 10% monocytes, 12% atypical lymphocytes, 7% neutrophils, and 3% basophils), 11 RBC/μl, elevated protein (209 mg/dl), glucose 40 mg/dl, and no organisms on Gram stain. The patient was empirically treated with vancomycin, ceftriaxone, and acyclovir until several days later, when the CSF HSV PCR was reported as positive for HSV-2. Vancomycin and ceftriaxone were discontinued, and the acyclovir was continued. A review of the patient's prior hospitalization at another institution revealed that in 2004 his CSF PCR had also been positive for HSV-2.

#### Case 2a Discussion: Herpes Simplex Virus Meningoencephalitis

Recurrent benign lymphocytic meningitis (RBLM) was first described in 1944 by the French neurologist, Pierre Mollaret. RBLM is not a chronic meningitis, but is a syndrome in which patients have recurrent episodes of aseptic meningitis.[1] When first described, Mollaret noted an increased level of "endothelial cells" in the CSF early in the disease, which he dubbed *Mollaret cells*. These large, granular cells have a monocytic/macrophage lineage.[1] They can appear early in the disease, or not at all, but eventually the predominant cells in the CSF become lymphocytes. Studies have shown a probable link between HSV (most commonly HSV-2) and RBLM—but other viruses, such as Epstein-Barr virus, coxsackievirus, and echoviruses, have been implicated as causes of recurrent meningitis. There is, however, limited data on these other viruses.[1–3] Rheumatological diseases have also been implicated.

#### Clinical Manifestations and Diagnosis

Approximately one-half of patients have transient neurological symptoms, including seizures, hallucinations, diplopia, cranial nerve palsies, or altered levels of consciousness.[1] These symptoms are transient and, if they persist, a diagnosis of RBLM should be excluded. Most symptoms resolve within 2–5 days, with recurrences seen weeks, months, or years later.[1]

The diagnosis of RBLM is a diagnosis of exclusion. In 1962, Bruyn proposed the clinical diagnostic criteria of: (1) recurrent episodes of severe headache, meningismus, and fever; (2) CSF pleocytosis with large "endothelial" cells, neutrophils, and lymphocytes; (3) attacks separated by symptom-free periods of weeks to months to years; (4) spontaneous remission of symptoms and signs; and (5) no causative etiologic agent detected.[4] Since the diagnostic criteria were proposed, studies have shown that patients can present without fever, without the typical Mollaret cells, and are often PCR positive for HSV.

HSV Type 1 and Type 2 establish latent infections in the peripheral nervous system of humans. Reactivation of latent HSV infection from sensory ganglia results in a broad range of clinical manifestations, depending on the site of latency, virus type, and immune competency of the host. HSV-2 latency occurs primarily in sensory neurons of sacral dorsal root ganglia. It is postulated that HSV-1 in trigeminal ganglia may spread to brain parenchyma, producing encephalitis, whereas HSV-2 in sacral dorsal root ganglia may seed the cerebrospinal fluid and produce meningitis.[1,2] Even when meningitis results from the reactivation of latent HSV-2 infection in patients with known genital herpes, coincident herpetic skin lesions are documented in less than 50% of cases; similarly, in HSV-1 encephalitis, mucocutaneous manifestations are seldom seen.[2,3]

In the largest study to date of patients who met the criteria for RBLM, they averaged 4.6 attacks of meningitis over 2–21 years, with attacks lasting 3–14 days.[2] CSF white blood cell counts ranged from 48–1600 cells/μl, with a lymphocytic predominance, normal glucose, and protein ranging from 41–240 mg/dl.[2] HSV was detected by PCR in 11/13 (84.6%), and 10/11 (91%) specimens were HSV-2.[2] Only 3 of 11 patients with HSV DNA and antibody in their cerebrospinal fluid had a history of recurrent genital HSV infection.[2]

#### Treatment

Because of the rarity of this syndrome, there are no large clinical trials comparing one therapy against another. Administration of intravenous acyclovir (10–15 mg/kg every 8 h for 7–10 days) has putatively resulted in rapid resolution of infection.[1] Valacyclovir and famciclovir have been used, as well. Steroids, colchicine, antihistamines, and phenylbutazone have been administered to patients with RBLM without reported benefit.[1] Other experts have advocated for no treatment, since the symptoms are often self-limiting. In cases of HSV encephalitis, a 21-day course of acyclovir (10–15 mg/kg every 8 h) is recommended. There is little data regarding the use of prophylaxis to prevent recurrence. In one instance, a 52-year-old woman who experienced 21 episodes of recurrent aseptic meningitis over 20 years began suppressive therapy with acyclovir; no other outbreaks were reported after treatment.[1] Prophylaxis should be weighed based on the frequency of recurrences.

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## Confusion and Fever in an Elderly Woman

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### Presentation and Case History

An 80-year-old woman with no known past medical history was brought to the emergency department because of confusion and bizarre behavior. Two days prior to admission, the doorman of the patient's building noticed the patient wandering the halls of the building in a confused, agitated state; according to the doorman, the patient is normally highly functional and manages her own affairs. On initial assessment, the patient was confused and unable to give a coherent history, stating, "I am fine. Who are you? Why am I here?" She denied any and all complaints and sick contacts, had no pets, and had not traveled outside of New York City in the last year.

On physical examination, the patient's temperature was 38.9° Celsius, heart rate was 92 beats per minute, blood pressure was 115/77, and respiratory rate was 18 breaths per minute; oxygen saturation on pulse oxymetry was 100% on ambient air. In general, she was a well-developed, well-nourished elderly woman in no apparent distress. She was delirious and confused and oriented to person only, but had no other focal neurological deficits. Her neck was soft and supple, mucous membranes were moist and oropharynx was clear, and the remainder of her physical examination was unremarkable.

Laboratory studies were notable for leukocytosis (12.5 × $10^3$ cells/μl), but all other studies including serum electrolytes, TSH, RPR, hemoglobin, and urinalysis were within normal limits. A chest X-ray and computed tomography (CT) of the head without intravenous contrast were unremarkable. A lumbar puncture was performed; CSF analysis showed a lymphocytic pleocytosis (65 WBC/μl, 1% neutrophils, 87% lymphocytes), protein 29 mg/dl, and glucose 71 mg/dl. CSF Gram stain, VDRL, and fungal stain were negative. A presumptive diagnosis of HSV meningitis was made, and IV acyclovir started. The patient's mental status improved and her fever resolved. On the third day of her hospitalization, the patient noted the appearance of a rash on the left side of her chest. The patient remembered that she had some itching in the area of the rash several days before her hospitalization. Examination revealed an erythematous, vesicular rash in a dermatomal distribution (Figure **2b.1**). The patient denied pain at the site of the rash, but complained of mild pruritus. The CSF PCR for varicella zoster virus (VZV) was reported as positive, giving a diagnosis of VZV encephalitis. The patient continued to improve and was discharged home in stable condition after receiving 7 days of intravenous acyclovir.



Figure 2b.1.
Left thorax with an erythematous, vesicular rash in a dermatomal distribution

#### Case 2b Discussion: Varicella Zoster Virus Encephalitis

Virology and Epidemiology

Varicella zoster virus is a member of the Herpesviridae family, and is the etiological agent of primary varicella infection (chicken pox) and herpes zoster. VZV infects sensory

nerve fibers during primary infection, and establishes permanent latency in neuronal bodies located in regional sensory ganglia. Herpes zoster is the manifestation caused by the reactivation of latent VZV, which leads to dermatomally restricted cutaneous disease ("shingles") or, less commonly, disseminated or visceral disease.

VZV is transmitted via the respiratory route, where it replicates in the nasopharynx or upper respiratory airways.[1] Patients with herpes zoster are infectious from the onset of the rash until the lesions crust; susceptible patients who are infected develop primary varicella infection. Transmission can be greatly reduced by covering the affected area. Patients should be asked to avoid contact with susceptible persons, particularly those at risk for complications (e.g., pregnant women, prematurely born infants, immunocompromised persons) until all of their lesions have crusted over.[2] Hospitalized persons who have disseminated zoster, or lesions that are difficult to cover, should be isolated using airborne and contact precautions. The use of masks and type of masks (e.g., surgical mask versus N95 respirator) used by either immune or susceptible healthcare workers is a subject of some debate, and should be decided in each institution by local infection control specialists.[3]

The main risk factor for herpes zoster is a history of primary varicella. Approximately 99.5% of the adult population over the age of 40 has serological evidence of prior infection, despite the fact that many will not remember a history of the chickenpox rash[3]; therefore, nearly all older adults are at risk for zoster. Age is an important risk factor, with significant increases occurring during the sixth decade of life (Figure **2b.2**). Approximately 50% of persons living to the age of 85 will experience at least one episode of herpes zoster.

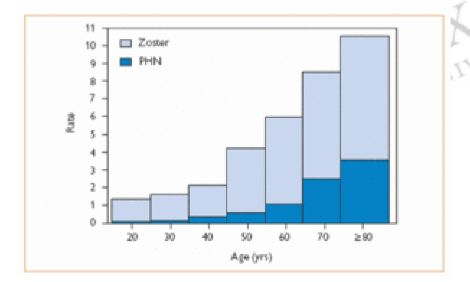



Figure 2b.2.
Rate of zoster and postherpetic neuralgia (PHN) by age—United States. Source: Centers for Disease Control and Prevention. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of Herpes Zoster. *MMWR.* May 15, 2008: 57;1–30.

The risk of reactivation is dramatically increased in immunocompromised hosts, especially those with deficits in T-cell mediated immunity (e.g., HIV, lymphoproliferative diseases, solid organ or bone marrow transplantation). Inflammatory diseases, such as systemic lupus erythematosis, rheumatoid arthritis, Wegener's granulomatosis, Crohn's disease, and ulcerative colitis, have also been associated with an increased risk of herpes zoster. It is unclear if this increased risk is related to the actual disease process, or to immunosuppressive medications that are used for treatment.[2]

Most complications of herpes zoster are related to the specific area of involvement. The most frequent complication is post-herpetic neuralgia (PHN), defined as the persistence of pain after resolution of skin lesions. The incidence of PHN in the pre-vaccine era was 18%, 13%, and 10% at 30, 60, and 90 days, respectively, after resolution of the rash. The incidence of PHN increases with age, and approximately 20% of patients over the age of 80 experience PHN three months after resolution of rash.[4] PHN can be debilitating, leading to loss of employment, depression, social isolation, and increased medical costs. Bacterial superinfection of the vesicular lesions, typically with normal skin flora, can also occur.

Herpes zoster ophthalmicus can affect almost all structures of the ipsilateral eye and requires immediate evaluation by an ophthalmologist, as well as prompt antiviral therapy to prevent loss of vision. Involvement of the mucocutaneous division of cranial nerve VII and/or VIII can lead to the Ramsey-Hunt syndrome, characterized by facial paralysis, associated hearing and vestibulatory symptoms, and vesicular lesions in the external auditory canal. Facial nerve involvement can occur without the presence of vesicular lesions. Other serious complications, such as encephalitis, meningitis, retinitis, myelitis, or death, are uncommon. They usually occur in immunocompromised hosts, but can affect persons with no obvious predisposing condition or medication-related deficit in cell-mediated immunity.

## Clinical Features

Herpes zoster is characterized by a painful vesicular rash in a unilateral, dermatomal distribution, with occasional involvement of two or three adjacent dermatomes. The pain is classically described as burning, throbbing, or stabbing, and is often associated with tactile hyperesthesia, though occasionally pruritus is the dominant complaint. Pain generally precedes the appearance of the rash by several days and, depending on the sensory dermatome involved, can be confused with other acute medical conditions, such as unstable angina, cholecystitis, or renal colic.

Although virtually any peripheral sensory nerve can be a source of reactivation, the most common sites in immunocompetent hosts are the thoracic sensory nerves, followed by the ophthalmic division of the trigeminal nerve (herpes zoster ophthalmicus). Herpes zoster rarely presents in atypical or severe forms, especially in patients with deficits in cell-mediated immunity. Examples include disseminated cutaneous disease (vesicles appearing at a distance or contralaterally from the original dermatome), meningoencephalitis, or visceral disease (e.g., pneumonitis, hepatitis, pancreatitis, etc.).[5,6]

VZV meningoencephalitis presents similarly to other causes of viral infections of the brain (e.g., headache, fever, photophobia, nausea, vomiting, and confusion).[1] The characteristic rash of herpes zoster often appears after the onset of CNS symptoms, though in some cases it can be the presenting symptom.[7,8] The rash can help distinguish the disease from other viral causes of meningoencephalitis, such as herpes simplex virus or West Nile virus.

## Diagnosis

Herpes zoster is typically a clinical diagnosis based on the characteristic appearance and distribution of the rash, associated symptoms, and time course of disease (Figure **2b.3**). In patients who present with an atypical rash or disseminated disease, VZV direct fluorescent antigen (DFA) testing of skin scrapings can provide a rapid diagnosis. Real-time polymerase chain reaction (PCR) can be performed on a variety of clinical samples, including CSF. The utility of viral culture is limited by a longer turnaround time.





Figure 2b.3.
Dermatomal rash with lesions in various stages: crops of vessicles with an erythematous base and other lesions that have crusted over.

Since patients with uncomplicated cutaneous herpes zoster will frequently have a headache, it is important that other symptoms associated with viral CNS infection, or risk factors for invasive disease, be present before aggressively pursuing the diagnosis of VZV meningoencephalitis. Some patients with uncomplicated herpes zoster may have a lymphocytic pleocytosis, even in the absence of overt encephalitis.[9] CSF sampling is critical for diagnosis of VZV meningoencephalitis, and for distinguishing this disease from other causes of invasive CNS disease. CSF analysis will reveal abnormalities consistent with other causes of viral meningoencephalitis: a lymphocytic pleocytosis, elevated protein, and occasionally decreased glucose. PCR for VZV can be performed on CSF samples; a positive result confirms the diagnosis.

## Treatment

Systemic antiviral therapy, specifically with acyclovir, famciclovir, or valacyclovir, is the mainstay of treatment and has been shown to reduce viral shedding, duration of rash, and PHN (see Table 2b.1).[6]

Table 2b.1 Oral Antiviral Medications for Herpes Zoster

| Medication | Dosage | Duration of treatment, days | Most common adverse effects | Precautions and contraindications |
|---|---|---|---|---|
| Acyclovir | 800 mg 5 times daily (every 4–5 h) | 7–10 | Nausea, headache | Dosage adjustment required for patients with renal insufficiency |
| Brivudin[a] | 125 mg once daily | 7 | Nausea, headache | Contraindicated for patients treated with 5-fluorouracil or other 5-fluoropyrimidines, because of drug interaction associated with severe and potentially fatal bone marrow suppression |
| Famciclovir | 500 mg 3 times daily (approved dosage in United States; in some other countries, 250 mg 3 times daily is approved) | 7 | Nausea, headache | Dosage adjustment required for patients with renal insufficiency |
| Valacyclovir | 1000 mg 3 times daily | 7 | Nausea, headache | Dosage adjustment required for patients with renal insufficiency; thrombotic thrombocytopenic purpura/hemolytic uremic syndrome reported at dosages of 8000 mg daily in immunocompromised patients |

[a] Not available in the United States.

Reprinted with permission from The University of Chicago Press. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the Management of Herpes Zoster. *Clinical Infectious Diseases.* 2007;44:S1–S26.

The duration of treatment is usually seven days, and valacyclovir is generally preferred because of its convenient dosing schedule. The most common side effects of these medications are nausea and headache. Dose adjustments are needed in patients with impaired renal function. Antiviral therapy is strongly recommended in immunocompetent patients with any of the following criteria:[6]

1. Age ⟩ 50
2. Non-truncal involvement
3. Moderate to severe pain and/or rash
4. Presentation within 72 hours of the onset of symptoms

Given their benign side-effect profile, many experts recommend considering the use of antivirals in all patients with herpes zoster, even those at low risk for severe complications or who present greater than 72 hours after the onset of symptoms.[6] Oral therapy is appropriate in most cases of herpes zoster. Intravenous acyclovir is recommended in patients with serious or disseminated disease, depressed cell-mediated immunity, or herpes zoster ophthalmicus.

Meningoencephalitis is a serious complication of herpes zoster and should be treated aggressively with intravenous therapy; therapy should be instituted immediately, as soon as this diagnosis is suspected, and not delayed while waiting for the results of confirmatory diagnostic tests (e.g., PCR). There are no good data evaluating oral therapy (e.g., with valacyclovir), but it may not be unreasonable to switch to oral therapy if the patient has a rapid therapeutic response to intravenous therapy after a few days. In both mild and serious cases of herpes zoster, there is little data to support a duration of therapy greater than 7 days. Herpes zoster can be prevented with administration of a live, attenuated vaccine. This vaccine has been shown to decrease the incidence of herpes zoster by 50% and to lower the risk of post-herpetic neuralgia by 67%. It is recommended for all patients over the age of 60, including patients who have had an episode of herpes zoster prior to vaccination.[2]

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 41-year-old Woodcutter with Progressively Worsening Mental Status

**Chapter:** A 41-year-old Woodcutter with Progressively Worsening Mental Status
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 41-year-old woodcutter presented to an outside facility with a 3-month history of generalized malaise, weakness, dyspnea, and productive cough that started one week prior to his presentation to another institution. The patient reported no history of hemoptysis or chest pain, but he had been having night sweats and rigors for three months. He was febrile on admission and was noted to have a scaly dry lesion on the right eyebrow. His mental status worsened at the initial hospital to the point that he required mechanical ventilation. The patient was discovered to have advanced AIDS when his HIV serology was reported as positive, and his CD4+ cell count was 4 cells/μl; his most likely risk factor was a remote history of drug abuse.

CT scan of the head revealed multiple brain lesions in the right cerebellum. A brain MRI revealed multiple T2 and FLAIR hyperintense lesions, the largest in the cerebellum with patchy T1 shortening, moderate mass-effect, and significant surrounding edema. Additional lesions were present in the left anterior frontal subcortical white matter and in the left medial temporal lobe. Diffuse leptomeningeal enhancement within the cerebellum and surrounding the brainstem was also evident (Figures **2c.1a through 2c.1d**). PET scan revealed markedly elevated FDG activity within both medial temporal bones, differential FDG activity in the cortex, and deep gray nuclei with a relatively increased FDG uptake in the deep gray nuclei and decreased FDG uptake in the cortex (Figure **2c.2**).

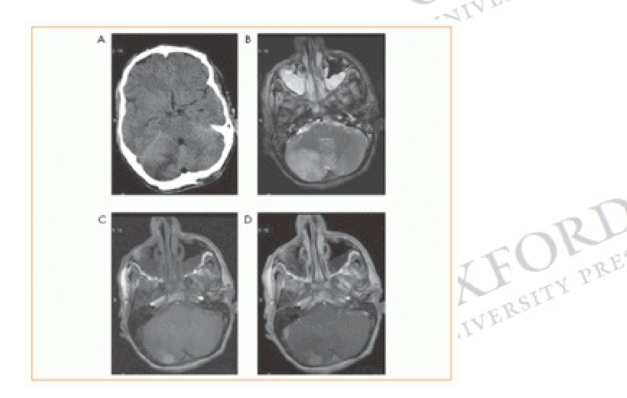





Figure 2c.1a through 2c.1d.
Non-contrast head CT demonstrating the right cerebellar hemisphere hypodense lesion with mild mass effect upon the fourth ventricle. T2 (B), T1 (C), and T1 postcontrast (D) axial head MR images demonstrating T2 and FLAIR hyperintense lesion in the right cerebellum with patchy T1 shortening, moderate mass-effect, and significant surrounding edema.

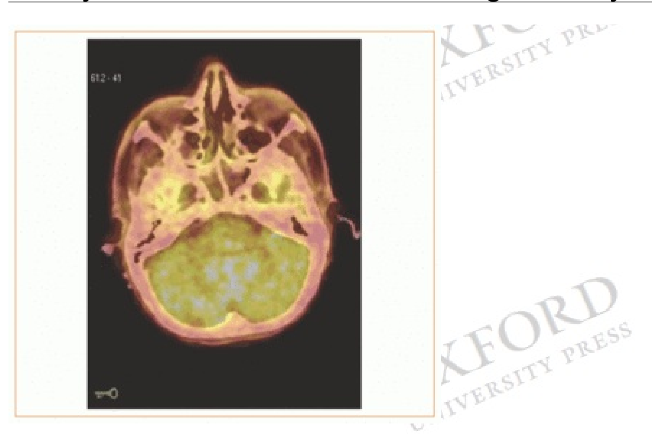





Figure 2c.2.
Positron Emission Tomography (PET) scan of brain showing hypometabolic lesion within the right hemisphere of the cerebellum.

Multiple laboratory studies, including urine *Histoplasma* antigen, CMV viral load, RPR, and cryptococcal serum antigen were all negative. CSF analysis revealed 10 WBC/µl with 1% neutrophils, 95% lymphocytes, protein 79 mg/dl, and glucose 72 mg/dl. JCV, EBV, HSV, and *Toxoplasma* were all negative on CSF analysis. Brain biopsy revealed cerebellar tissue with numerous macrophages engulfing intracytoplasmic amebas with prominent nuclei and karyosomes (Figures **2c.3a through 2c.3d**).

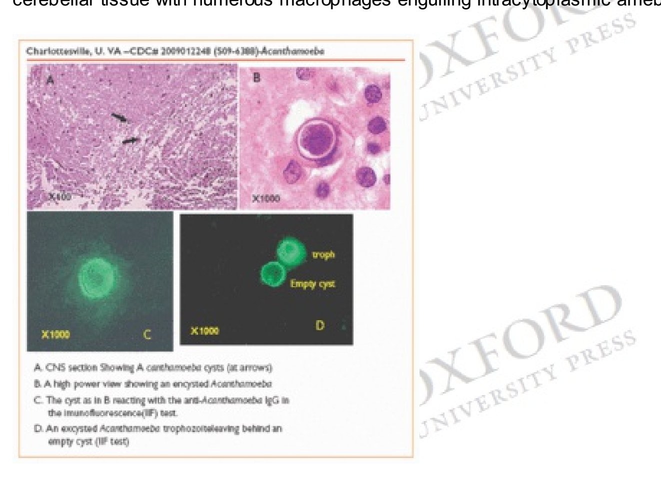






Figure 2c.3a through 2c.3d.
(A) Brain biopsy showing Acanthamoeba cysts, hematoxylin and eosin stain; (B) Brain biopsy with encysted Acanthamoeba, hematoxylin and eosin stain; (C) Brain biopsy with encysted Acanthamoeba, immunofluorescence stain; and (D) Brain biopsy with Acanthamoeba trophozoite and cyst, immunofluorescence stain.

The differential diagnosis included infection with *Acanthamoeba* spp., *Balamuthia mandrillaris*, and *Naegleria fowleri*. Given the presence of a double-contoured cyst wall and the appearance of the nuclei and karyosomes, the pathologist in our institution favored *Balamuthia* as the etiologic agent. *Naegleria fowleri* was thought to be unlikely, given that the encysted form is not usually identified in histologic sections. With the pathology results suggestive of *Balamuthia mandrillaris* infection multiple antimicrobials with in vitro activity against free-free living amebas were initiated. The patient remained unresponsive when not sedated and ventilator-dependent despite multiple antimicrobials that have been found to have in vitro activity against free living amebas. It was decided to pursue only palliative measures. He died soon thereafter.

The indirect immunofluorescence on brain tissue performed at the CDC was later found to be positive for *Acanthamoeba sp* (Figures **2c.3 c**,**d**). Real-time PCR on CSF was also positive for *Acantamoeba*, negative for *Balamuthia mandrillaris* and *Naegleria fowleri.* Serologic testing using indirect immunofluorescence antibody was negative for both *Acanthamoeba* and *Balamuthia mandrillaris*. Postmortem examination confirmed amoebic encephalitis involving the parenchyma of the cerebellum and cerebrum with dissemination through the ventricles and cerebrospinal fluid, and brain PCR was positive for *Acanthamoeba sp.*

**Case 2c Discussion: *Acanthamoeba* Encephalitis**

## Diagnosis and Clinical Features

Free living ameba of the genus *Acanthamoeba* are found in the environment worldwide, and are responsible for disease mainly in immunocompromised patients, but cases of amebic infection due to *Acanthamoeba* have been described in adults and children with no underlying conditions.[1–4] *Acanthamoeba spp* with *Balamuthia mandrillaris* are the causative agents of granulomatous amebic encephalitis (GAE), a subacute CNS infection characterized by insidious onset of symptoms over a period of time that varies from weeks to months. Patients may present with headache, confusion, nausea, vomiting, low-grade fever, lethargy, focal neurologic deficits, or signs of increased intracranial pressure.[2,4] The prognosis of GAE is very poor; death usually occurs from brain herniation due to increased intracranial pressure. Humans are presumably infected by direct inoculation via nasal passages, pulmonary inhalation, or introduction through skin lesion and dissemination to the brain, possibly via hematogenous spread.[4]

The clinical diagnosis is difficult and the definitive diagnosis is usually achieved by brain biopsy, often not until postmortem exam. The pathogenesis of the infection is poorly understood; severe hemorrhagic necrosis, fibrin thrombi, and subacute granulomatous encephalitis are found on pathology. Tissue examination may reveal numerous trophozoites and cysts, and granulomas may be scarce or absent in immunocompromized hosts.[4] CSF analysis is not pathognomic and can reveal lymphocytic pleocytosis, slight increased protein, and normal or mildly decreased glucose.[1] In case of high index of suspicion, trophozoites may be observed on Wright-Giemsa stain and wet mount preparation of CSF.[5] The organism can be detected by immunofluorescence staining, and PCR can detect *Acanthamoeba* DNA; serology can be done by indirect immunofluorescence.[2,5] CT scans in different cases have shown enhancing lesions and multifocal lesions, edema; multiple ring enhancing lesions may be observed on MRI.[2,6]

## Treatment

Treatment of GAE is challenging, because diagnosis is often delayed and because the organism is generally poorly responsive to therapy once there is CNS involvement. Many combinations of different agents have been tried based on in vitro activity. These have included trimethoprim-sulfamethoxazole, rifampin, miltefosine, amphotericin, pentamidine, etc., but none have been demonstrated to have satisfactory outcome in late-stage disease.

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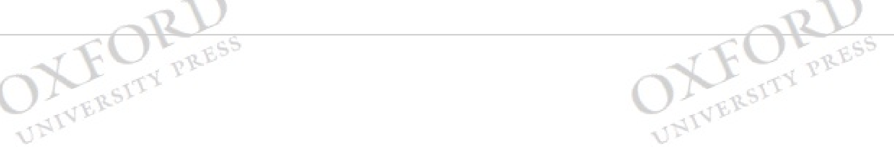
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# A Renal Transplant Recipient with Weakness and Gait Instability

**Chapter:** A Renal Transplant Recipient with Weakness and Gait Instability
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0009

### Clinical Presentation

A 38-year-old man from Romania was admitted with numbness and tingling in both legs, as well as unsteady gait. One day prior to admission he noted difficulty getting up from a chair, and eventually he had difficulty ambulating and walking up stairs. He also began experiencing numbness and tingling in both legs. Upon further questioning, he admitted that over the past six months he had noticed feeling a bit more "clumsy," but attributed this to lack of exercise. He denied any fevers or chills, visual changes, cough, dyspnea, abdominal pain, diarrhea, or rash.

He had undergone renal transplantation for glomerulonephritis, in Romania, 25 years earlier. He underwent a second renal transplant for chronic rejection in Oregon, seven years prior to presentation. His immunosuppressive medications included cyclosporine, mycophenolate mofetil, and prednisone. He was born in Romania but had lived in the United States for 20 years, and had not recently traveled. He had no pets or sick contacts.

On physical examination, the patient had no fever, photophobia, or nuchal rigidity. His neurologic exam was significant for decreased lower extremity strength (4/5), hypertonicity, and hyperreflexia in both legs and sustained ankle clonus on the right. He had decreased sensation to light touch pinprick and vibration in both legs, as well as a spastic gait and a positive Romberg sign. In addition, he had a right foot drop and a positive plantar reflex on the right. The remainder of the physical examination was unrevealing. His admission laboratory values, including tests for HIV and syphilis, were nondiagnostic. MRI of the brain with gadolinium was normal, but MRI of the spine revealed cord atrophy at T4–11 (Figure **2d.1**). Cerebrospinal fluid analysis revealed 27 white blood cells (88% lymphs, 12% mono), increased protein (78 mg/dl), and normal glucose (82 mg/dl). No organisms were found on Gram stain, acid fast stain, or fungal stains of the CSF. Cerebrospinal fluid tests for CMV, HSV-1/2, VZV, EBV, HHV-6, West Nile virus, *Toxoplasma*, Lyme, lymphochoriomeningitis virus, and Cryptococcus were all negative. HTLV-1 (human T-lymphotropic virus) DNA was detected by PCR of the CSF, however, and the patient was diagnosed with HTLV-1 associated myelopathy. Upon further investigation, it was discovered that the second donor kidney had been harvested from a cadaveric donor who was originally from the Caribbean.

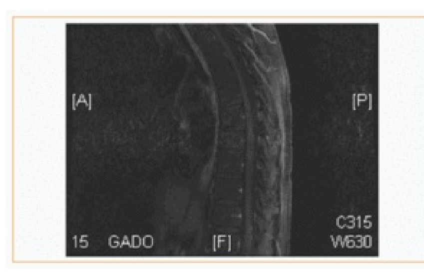







Figure 2d.1.
MRI spine (sagittal view) showing mild spinal cord atrophy at T4–11.

#### Case 2d Discussion: Human T-lymphotropic virus-1 Myelopathy

Epidemiology

It is estimated that between 10 and 20 million people worldwide are infected with HTLV-1. Certain geographic areas are endemic for infection, such as southern Japan and the Caribbean. Rates of seropositivity in Jamaica, Trinidad and Tobago, Barbados, Haiti, and the Dominican Republic range between 5% and 14%. HTLV-1 is also present in South and Central America, including Brazil (especially Bahia and the northeast), Colombia, Venezuela, Guyana, Surinam, Panama, and Honduras.

In the United States, large-scale blood supply screening has documented rates of HTLV-I/II of 0.3 to 0.4 per 1000, of which one-third to half of these are HTLV-1.[1] Evidence suggests that most of these donors had links to an endemic area, or an exposure risk such as blood transfusion or multiple sexual partners. Seroprevalence tends to increase

with age, and women are nearly twice as likely as men to be infected, a phenomenon likely related to higher efficiency of sexual transmission from male to female.[2,3] As HTLV-1 infection is more prevalent in women, the incidence of HAM/TSP is also more common. It affects less than 2% of HTLV-1 carriers, and the onset ranges from 4 months to 30 years, with a median of about 3 years after infection.

The primary mode of transmission of HTLV-1 is breastfeeding. Virus is found in breast milk, and animal studies have confirmed transmission.[4] Human epidemiologic studies have shown that breastfed infants have a fourfold increased risk of infection versus bottle-fed infants, and the longer a mother breastfeeds, the higher the risk of transmission.[5] There is likely a transient protective effect of maternal antibodies transferred in utero.[6] While breast milk is the principal mode of HTLV-1 transmission, it can also be spread via sexual intercourse, blood transfusion, and shared needles, as well as vertically during birth.

## Donor-Derived HTLV-1 in Organ Transplantation

Finally, an area that deserves special attention due to our case is donor-derived infections during solid organ transplantation. It is not known whether HTLV infection contributes to significant morbidity in solid organ recipients. Obviously, donor-derived transmission and infection can simply lead to seroconversion in the organ recipient, as in nontransplant hosts, without evidence of the patient ever developing clinical disease. However, seroconversion and evolution of disease years later has been reported, with HTLV-1-associated myelopathy being reported in a previously seronegative recipient 4 years after cadaveric renal transplantation.[7] In another series, three recipients of solid organ transplants (one liver, two kidney) developed a subacute myelopathy within 2 years after becoming infected with HTLV-I from a single asymptomatic HTLV-I donor.[8] Despite these case reports, UNOS (*United Network for Organ Sharing*) data suggests that transmission of virus leading to morbidity is rare, and that HTLV-positive donors should be considered. In 25 seropositive donors found from 1988–2000, with 22 organs transplanted, there were no cases of HTLV-related disease reported in recipients, with a median nearly 12 months of follow-up.[9]

## Clinical Presentation

HTLV-1 infection has a broad range of manifestations. The vast majority of patients who are HTLV-1 seropositive are asymptomatic. The virus infects T cells and can lead to smoldering or aggressive adult T-cell lymphoma/leukemia. Defects in cellular immunity can lead to increased risk for relapsing strongyloidiasis and infective dermatitis. HTLV-1-associated myelopathy is a disease of insidious onset, in which patients experience slowly progressive weakness and spasticity of one or both legs. Other manifestations include hyperreflexia, ankle clonus, extensor plantar responses, and lumbar pain. The upper extremities are spared, but genitourinary symptoms are common, including detrusor instability leading to nocturia, urinary frequency, and incontinence. There are also minor sensory changes, especially paresthesias and loss of vibration sense, but cognitive function is unaffected. HTLV-1 infection can also lead to a spectrum of other neurologic abnormalities besides myelopathy, including generalized leg weakness, impaired tandem gait, urinary incontinence, and impaired vibration sense.

## Diagnosis

Diagnostic criteria were agreed upon by a World Health Organization (WHO) panel in 1989 (See Table 2d.1).[10]

Table 2d.1 WHO Diagnostic Criteria for TSP/HAM

**I.** Clinical criteria
The florid clinical picture of chronic spastic paraparesis is not always seen when the patient first presents. A single symptom or physical sign may be the only evidence of early HAM/TSP.

- **A.** Age and sex incidence
  Mostly sporadic and adult, but sometimes familial; occasionally seen in childhood; females predominant.
- **B.** Onset
  This is usually insidious but may be sudden.
- **C.** Main neurological manifestations
  1. Chronic spastic paraparesis, which usually progresses slowly, sometimes remains static after initial progression.
  2. Weakness of the lower limbs, more marked proximally.
  3. Bladder disturbance usually an early feature. Constipation usually occurs later; impotence or decreased libido is common.
  4. Sensory symptoms such as tingling, pins and needles, burning, etc. are more prominent than objective physical signs.
  5. Low lumbar pain with radiation to the legs is common.
  6. Vibration sense is frequently impaired; proprioception is less often affected.
  7. Hyperreflexia of the lower limbs, often with clonus and Babinski's sign.
  8. Hyperreflexia of upper limbs; positive Hoffmann's and Tromner signs frequent; weakness may be absent.
  9. Exaggerated jaw jerk in some patients.
- **D.** Less frequent neurological findings
  Cerebellar signs, optic atrophy, deafness, nystagmus, other cranial nerve deficits, hand tremor, absent or depressed ankle jerk.
  Convulsions, cognitive impairment, dementia, or impaired consciousness are rare.
- **E.** Other neurological manifestations that may be associated with HAM/TSP Muscular atrophy, fasciculations (rare), polymyositis, peripheral neuropathy, polyradiculopathy, cranial neuropathy, meningitis, encephalopathy.
- **F.** Systemic nonneurological manifestations that may be associated with HAM/TSP Pulmonary alveolitis, uveitis, Sjögren's syndrome, arthropathy, vasculitis, ichthyosis, cryoglobulinemia, monoclonal gammopathy, adult T-cell leukemia/lymphoma.

**II.** Laboratory diagnosis

- **A.** Presence of HTLV-1 antibodies or antigens in blood and cerebrospinal fluid (CSF).
- **B.** CSF may show mild lymphocyte pleocytosis.
- **C.** Lobulated lymphocytes may be present in blood and/or CSF.
- **D.** Mild to moderate increase of protein may be present in CSF.
- **E.** Viral isolation when possible from blood and/or CSF.

Reprinted with permission from WHO. Virus Diseases: Human T lymphotropic virus type I, HTLV-I. Wkly Epidemiol Rec 1989; 64:377–384.

MRI of the brain and spinal cord can be normal, but may reveal atrophy of the cervical or thoracic cord and/or white matter lesions in the subcortical and periventricular regions. Neurophysiologic studies may reveal evidence of posterior column dysfunction, as well as a peripheral neuropathy.

## Management and Prognosis

There is no effective antiviral therapy for the treatment of HAM/TSP. Case series suggest that immunosuppressant medications such as corticosteroids may help to slow progression of disease and reduce neurologic disability. There are, however, no randomized clinical trials evaluating this, and so this therapy remains controversial.

Combination therapy with the nucleoside analogs, zidovudine and lamivudine, was evaluated in a randomized double-blind, placebo-controlled study, which included 16 patients with HAP/TSP, but no significant clinical improvement was noted after 12 months of follow-up.[1] The prognosis for patients affected by HAP/TSP is poor. One series of 123 affected patients demonstrated progression of disease from onset to wheelchair confinement occurring over a median of 21 years.[2]

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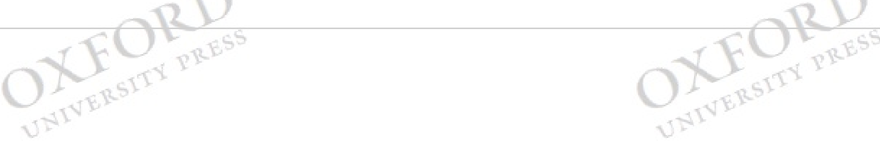
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# Ataxia, Dizziness, and Altered Mental Status in a Patient Previously Treated for Pneumonia

**Chapter:** Ataxia, Dizziness, and Altered Mental Status in a Patient Previously Treated for Pneumonia
**Author(s):** Daniel Caplivski and W. Michael Scheld
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## Case Presentation

A 70-year-old man with a history of hypertension, atrial fibrillation, and hyperlipidemia presented with a 4-day history of dizziness and falls to his left side. Three weeks prior to presentation, he was evaluated at an outside hospital for fever, chills, productive cough, and dyspnea. He was treated with levofloxacin for possible pneumonia and his cough had since resolved.

On physical examination, he was febrile (101.8° F), confused, and unable to cooperate with a full neurologic evaluation. There was a 2/6 systolic ejection murmur heard along the left sternal border, and rales at the lung bases bilaterally. The remainder of his physical examination was unrevealing. Laboratory analyses were notable for elevated erythrocyte sedimentation rate (86 mm/h) and normal C-reactive protein (0.5 mg/dl) with normal complete blood count and electrolytes.

CT of the head demonstrated a mass in the right occipital and temporal lobes, with adjacent edema leading to mass-effect of the right lateral ventricle. Brain MRI further clarified the lesion as multilobulated with an additional inferior satellite lesion (Figures **3a.1a and 3a.1b**, and Figure **3a.2**). Purulent material (10 cc) was drained through a burr hole approach, and cultures were positive for *Streptococcus intermedius*. His initial antibiotics (cefepime, vancomycin, and metronidazole) were narrowed to ceftriaxone and metronidazole when cultures returned *Streptococcus intermedius*. A CT of the chest was performed, which demonstrated a small pulmonary lesion, suspicious for an abscess.

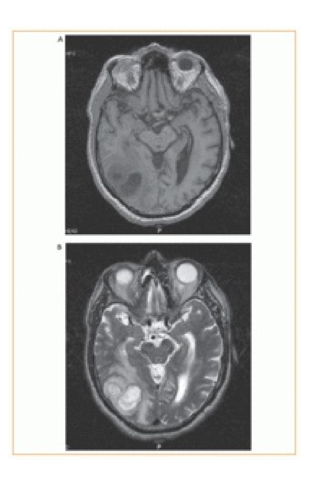


Figure 3a.1a and 3a.1b
Brain MRI (axial view) showing a right occipitotemporal lobe complex cerebral abscess due to *S. intermedius* with associated edema on T1 (A) and T2 (B) weighted imaging.

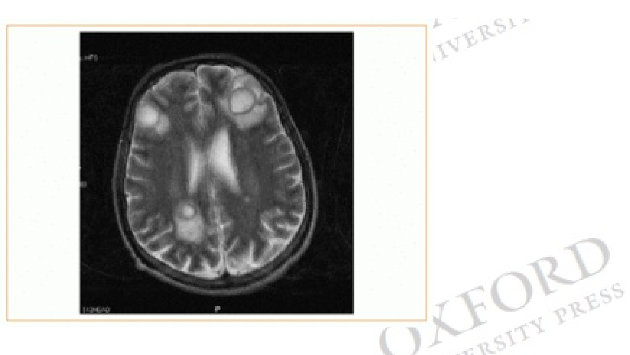


Figure 3a.2
Brain MRI (axial view) showing multiple cerebral abscesses with surrounding edema on T2 weighted imaging in a different patient with *S. intermedius* bacteremia.

**Case 3a Discussion: *Streptococcus intermedius* Brain Abscess**

## Clinical Presentation and Diagnosis

Brain abscesses are focal, space-occupying, purulent infections of brain parenchyma. Patients with brain abscess usually present with headache, confusion, and focal neurologic signs (e.g., weakness, aphasia, ataxia), but fever is reported in ≤50% of cases.[1,2] Patients with known brain abscesses who experience a sudden worsening of headache may have abscess rupture with associated ventriculitis. Elevated, normal, or decreased peripheral white blood cell counts may be present. Lumbar puncture is not necessary with suspected brain abscess, and poses a risk of brain herniation, but on CSF analysis approximately 60% of patients have pleocytosis, increased protein, and/or hypoglycorrhachia.[3] Low Glasgow Coma Scale (GCS), immunodeficiency, and presence of an underlying malignancy are poor prognostic factors.[3]

Advances in the antimicrobial and surgical treatment of sinonasal and orofacial infections, along with improvements in radiography (e.g., CT/MRI) for earlier detection, have decreased the mortality rate of cerebral abscesses from 60% during the 1970s to 10%–32%.[3] The predisposing condition leading to abscess formation predicts the focus of cerebral infection and presenting signs. Otogenic spread more often affects the temporal lobes (seizures) and cerebellum (ataxia), whereas sinonasal disease more often affects the frontal lobes (headache, personality changes, inattention). Trauma or surgery can lead to infection at the site of cranial defect.[2] Hematogenous spread can lead to multiple brain abscesses in varying locations. Endogenous infection most commonly arises from pyogenic sources within the thoracic or intra-abdominal cavities, particularly in patients with endocarditis or congenital cyanotic heart disease. In up to 40% of cases, no source is identified.[3]

Most bacterial cerebral abscesses are due to aerobic, anaerobic, and microaerophilic streptococci (up to 70%). The *Streptococcus anginosus* group (*S. anginosus*, *S. constellatus*, and *S. intermedius*) is particularly associated with brain abscess, and *S. intermedius* is the most frequently identified species.[1] Animal models demonstrate that members of this group grow better in an acidic abscess environment, and that anaerobic organisms promote the growth of streptococci. Clinical studies in both immunocompetent and immunocompromised patients indicate that 45%–60% of *S. anginosus* infections are mixed.[4,5] *Staphylococcus aureus* and *Staphylococcus epidermidis*, enterobacteriaceae, *Pseudomonas*, anaerobic bacteria (e.g., *Peptostreptococcus, Bacteroides, Prevotella*), *Mycobacterium tuberculosis*, and higher order bacteria (*Actinomyces* and *Nocardia*) are well-recognized causes of bacterial abscesses. *S. aureus* causes 10%–20% of all cerebral abscess cases, and is the most common cause of trauma and postsurgical cases.[1] Diagnosis relies on radiographic findings, as well as tissue for culture and pathology. Computed tomography with contrast localizes cerebral areas of enhancement, as well as sinus and mastoid origins, but MRI has a higher sensitivity and can identify cerebral abscesses during early stages of infection.[1] Stereotactic or open drainage for culture provides valuable diagnostic information as well as therapeutic advantage, when compared to empiric antimicrobial therapy without drainage.

## Treatment

Successful treatment depends on a combined surgical and medical approach, with culture results guiding antimicrobial choice; medical therapy without surgical intervention is associated with a poor outcome.[3] It is ideal for drainage and culture to be performed prior to the initiation of antibiotics, but this is often not possible due to concomitant sepsis or risk of herniation. Initial empiric regimens for community-acquired, traumatic, or nosocomial-acquired brain abscesses can include a third- or fourth-generation cephalosporin combined with metronidazole. The addition of vancomycin is particularly advisable in post-neurosurgical and post-trauma cases. Since anaerobic cultures have low sensitivity, a negative anaerobic culture does not exclude their involvement, and antimicrobial activity against them should be continued.

Intravenous therapy is recommended for 6–8 weeks followed by 2–6 months of an appropriate oral antibiotic that achieves adequate CNS levels.[1] In cases of nocardiosis, sulfonamides are the drug of choice, but combination therapy with an aminoglycoside, fluoroquinolone, carbapenem, or cephalosporin is recommend in immunocompromised patients and those with progressive disease.[2] Therapy for *Nocardia* abscesses requires at least 3–12 months of treatment, and possibly longer in immunocompromised patients (see case 3c). Adjunctive corticosteroid use is controversial, but recommended for patients with significant edema, increased intracranial pressure, or a predisposition to herniation. Antiepileptic medications should be used for patients who have experienced seizures, and antibiotics that predispose patients to seizures should be avoided. MRI after surgical and medical therapy may be used for assessment of therapeutic success, but abscess resolution may lag behind clinical improvement.

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

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## A 55-Year-Old Man with Back Pain

**Chapter:** A 55-Year-Old Man with Back Pain
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 55-year-old man with a history of diabetes, hypertension, and coronary artery disease presented to an outside facility with low back pain. He had an extensive history of disseminated MRSA infections that began 6 months prior to presentation with osteomyelitis of the right foot. He required amputation of the right hallux, and blood cultures and wound cultures from the operating room were positive for MRSA. Despite treatment with intravenous vancomycin he returned with lower back pain radiating to the right leg. He denied any weight loss, night sweats, or fever, and did not note any numbness or tingling in the lower extremities. His back pain was unremitting, however, and he was found to have an L4–5 discitis, epidural collection, and psoas abscess on lumbar spine MRI (Figure **3b.1**). In addition to ongoing vancomycin therapy using appropriate weight-based dosing (15 mg/kg intravenously with trough goals of 15–20 µg/ml), the patient was also treated with rifampin given the progressive nature of his infection.

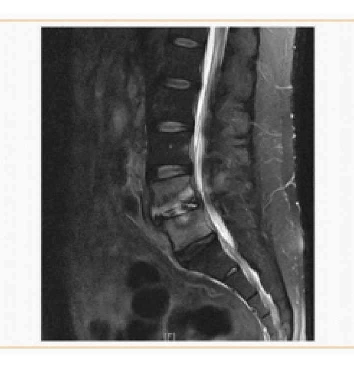





Figure 3b.1
MRI lumbar spine, sagittal view showing L4–5 osteomyelitis and discitis.

On physical examination, he was afebrile and had no focal neurologic deficits, but did have a positive straight leg test on the right. His laboratory findings were significant for the elevated erythrocyte sedimentation rate (132 mm/hour) and C-reactive protein (44). He underwent surgical debridement of the abscesses, L4-L5 anterior decompression, partial corpectomy, and allograft reconstruction. Culture of the abscess was sterile, but he was treated again with 6 weeks of intravenous vancomycin.

### Case 3b Discussion: *Staphylococcus aureus* Epidural Abscess

#### Clinical Presentation and Diagnosis

Spinal epidural abscesses are infections of the space between the dura and vertebral column. They are usually the result of hematogenous spreading from other infected sites, or direct local invasion. Sources of bacteremia include skin infections, urinary tract infections, endocarditis, pneumonia, periodontal abscesses, intravenous drug use, and indwelling venous catheters. Infections from local space invasion occur through procedures, including epidural anesthesia, lumbar puncture, and back surgery, or local infections, such as sacral decubitus ulcers and vertebral osteomyelitis. In 20%-40% of cases, the exact source cannot be identified. A major risk factor for disease is an immunocompromised state, including diabetes mellitus.[1] The organisms most frequently recovered include *Staphylococcus aureus* in 50%–90% of cases, streptococci in 8%–17% of cases, and Gram negative bacilli in 12%–17% of cases. The differential diagnosis for spinal lesions also includes *Nocardia spp.*, dimorphic fungi, *Mycobacterium tuberculosis*, and fungi.

The clinical presentation of spinal epidural abscesses includes back pain that may be acute or chronic. Acute presentation occurs over hours to days, and is typically associated with hematogenous seeding. Chronic symptoms develop over weeks to months, and are more common in the setting of contiguous foci of infection (i.e., vertebral

osteomyelitis). Fever is reported in 30%–60% of cases, but may be notoriously absent. Clinical symptoms may evolve from focal back pain to sensory and/or motor deficits, and ultimately complete paralysis. Prompt recognition is vital, since neurologic deficits are potentially reversible with treatment before paralysis develops.

Physical examination is often notable for focal spinal tenderness and neurologic deficits of involved spinal cord levels. Pertinent laboratory studies reveal an elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The diagnosis of epidural abscesses is confirmed with spine imaging. Magnetic Resonance Imaging (MRI) with gadolinium-contrast enhancement yields higher resolution images than computed topography (CT) scanning. MRI is superior at detecting associated osteomyelitis and discitis, and the presence of hyperintense signal on T2-weighted images may allow for differentiation of infected versus sterile collections. MRI may also be used to assess treatment response; however, radiologic changes often lag behind clinical cure.[1]

Cranial epidural abscesses are usually the result of an extension of infection from sinus, mastoid, and/or middle ear infections. Infection may also result from procedures such as craniotomy, and trauma can be a direct mechanism of infection. Cranial epidural abscesses present with headache in the absence of other symptoms, but a delay in diagnosis can lead to enlargement of the abscess with resulting focal neurologic symptoms and seizures. Physical examination may reveal neurologic deficits and signs associated with increased intracranial pressure, such as papilledema. Complications of a cranial epidural abscess include subdural empyema, brain abscess, and meningitis.

## Management

Epidural abscesses, both spinal and cranial, require a combination of medical and surgical therapy. Cranial epidural abscess requires a minimum of 3–6 weeks after surgical drainage, with a minimum of 6 weeks duration if osteomyelitis is evident. For surgical evacuation, craniectomy is preferred over burr hole placement. Spinal epidural abscess is treated for a minimum of 6–8 weeks after surgical debridement; the risk of relapse is decreased with 8 weeks of therapy.[1] Empiric antimicrobials such as vancomycin and third-generation cephalosporins are directed against *Staphylococcus aureus* and the Gram-negative organisms most frequently isolated in this disease. Newer anti-Staphylococcal agents such as daptomycin have been used for epidural abscess treatment, though large scale trials are lacking.[2] In post-neurosurgical infections, empiric therapy should account for local hospital epidemiology and antimicrobial resistance. Dorsal lesions are more likely than ventral lesions (30% versus 7%) to present with quadriplegia or paraplegia.[3] Patients with neurologic deficits require emergent surgical decompression with stabilization to prevent permanent damage. The mortality rate of epidural abscesses is 5%–23%, and neurologic presentation before surgical intervention is a major predictor of permanent neurologic sequelae.[4,5]

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## A Bone Marrow Transplant Recipient with Back Pain and Weakness

**Chapter:** A Bone Marrow Transplant Recipient with Back Pain and Weakness
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### Case Presentation

A 39-year-old man with a history of allogeneic bone marrow transplantation for acute myelogenous leukemia presented with several months of worsening lower extremity weakness, back pain, and dry cough. He received the bone marrow transplant from a closely matched sibling donor two years prior to presentation; however, his leukemia had subsequently relapsed. He was originally a farmer from rural Mexico, but had been working as a cook in New York for five years. Previous evaluations of his symptoms had revealed a lumbar paraspinal mass, and several left lower lobe pulmonary nodules. Biopsies of the paraspinal mass had revealed only acute inflammation, necrotic tissue, and sterile cultures. His medications included prednisone, voriconazole, ciprofloxacin, atovaquone, and valacyclovir.

On physical examination, he was febrile to 103° Fahrenheit, and had decreased strength and diminished reflexes in bilateral lower extremities. His pulmonary examination was unremarkable. Laboratory findings were significant for leukopenia ($2.6\times10^3$ WBC/μl, 24% neutrophils, 4% blasts), anemia (hemoglobin 8.4 grams/dl), and thrombocytopenia ($23\times10^3$ platelets/μl). A dense left lower lobe consolidation with areas of necrosis was seen on chest CT (Figure **3c.1**). Lumbar spine MRI revealed a worsening epidural abscess at the level of L3-L4, with collapse of the vertebrae and increasing compression of the thecal sac and cauda equina. There were also paraspinal components of the abscess involving the psoas and paraspinal muscles (Figure **3c.2**). Brain imaging did not reveal any focal abnormalities

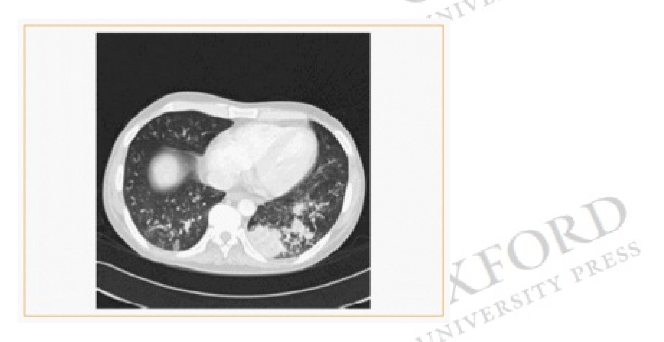




Figure 3c.1
CT lungs, axial view showing left lower lobe nodular consolidation.





Figure 3c.2

MRI spine, sagittal view showing epidural abscess at the level of L3-L4 with collapse of the vertebrae and increasing compression of the thecal sac and cauda equina. There were also paraspinal components of the abscess involving the psoas and paraspinal muscles.

Neurosurgical drainage of the abscess was performed, and cultures eventually yielded a Gram-positive, filamentous, branching rod with dry colonies that was identified as *Nocardia farcinica* (Figures **3c.3**, **3c.4**, **3c.5**).

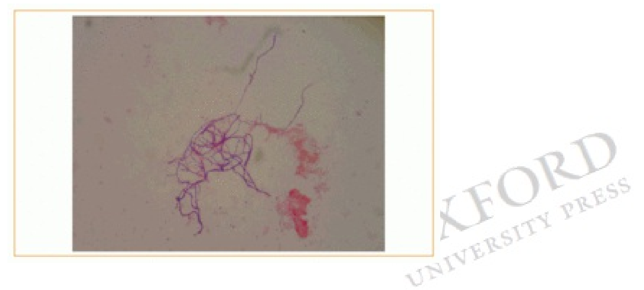


Figure 3c.3
Gram stain of lung biopsied material showing filamentous, beaded, branching Gram-positive bacilli.

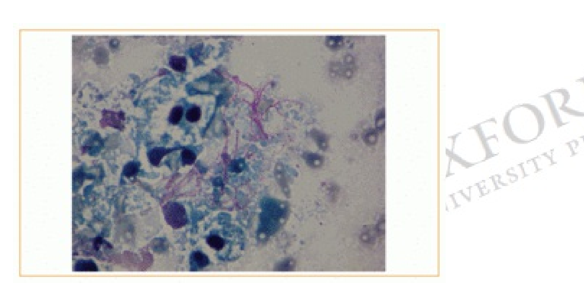




Figure 3c.4
Modified acid fast stain of biopsied material showing filamentous bacilli.

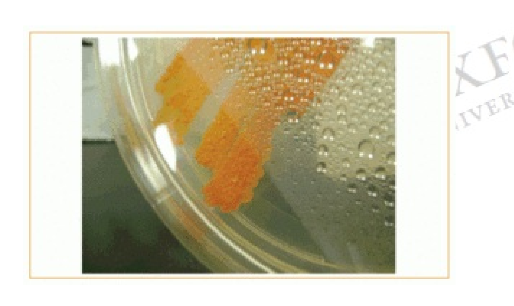
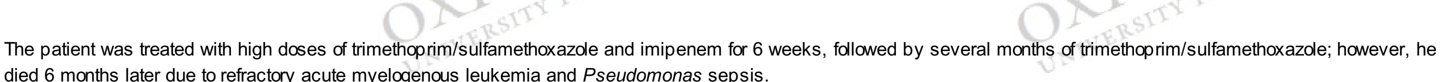




Figure 3c.5
Dry, pigmented colonies of *Nocardia farcinica* on Sabaroud's dextrose agar.



The patient was treated with high doses of trimethoprim/sulfamethoxazole and imipenem for 6 weeks, followed by several months of trimethoprim/sulfamethoxazole; however, he died 6 months later due to refractory acute myelogenous leukemia and *Pseudomonas* sepsis.

**Case 3c Discussion: *Nocardia farcinica* Epidural Abscess**

## Clinical Features and Diagnosis

*Nocardia* are aerobic, Gram-positive bacilli in the order *Actinomycetales.* They are ubiquitous, soil-dwelling bacteria, yet they are an uncommon etiology of localized and systemic suppurative infections in immunosuppressed and, to a lesser extent, immunocompetent human hosts. More than 50 species comprise the genus *Nocardia*; human disease is most often caused by the *Nocardia asteroides* complex, including *N. asteroides* sensu stricto, *N. farcinica*, *N. nova*, and *N. cyriacigeorgica.* Other species causing human infections include *N. brasiliensis*, *N. pseudobrasiliensis*, and *N. otitidiscavarium* (formerly *N. caviae*). Species have varying geographic distributions, which influences the most common species identified in single-center case series.[1,2]

Risk factors for nocardiosis include solid organ and bone marrow transplantation, the acquired immune deficiency syndrome (AIDS), glucocorticoid use, malignancy, and pulmonary disease.[1] The lungs are the most common site of infection with *Nocardia spp.*, followed by skin and soft tissues, the central nervous system (CNS), and other sites, including bones, kidneys, bloodstream, lymphatics, and lymph nodes.[1,2]

In disseminated infection, *Nocardia spp.* have an observed tendency toward invasion of the CNS, where they can persist for months or even years prior to diagnosis, long after the primary focus of infection is no longer evident. Brain abscess is the most common finding; however, diffuse cerebral inflammation, meningitis, and epidural abscess have also been reported, as well as vertebral osteomyelitis, discitis, and psoas abscess.[3] The presentation depends on the CNS site involved; clinically, findings can range from silent infections discovered incidentally on brain imaging or at autopsy, to acute, rapidly evolving mass lesions associated with a localizing constellation of neurological findings. Signs of systemic infection, like fever and leukocytosis, may be present or absent.[4]

## Management

Despite a lack of controlled clinical trials, sulfonamides like trimethoprim-sulfamethoxazole (TMP-SMX) have traditionally been the treatment of choice for *Nocardia* infections, based on retrospective data.[5] Other intravenous antibiotics used against *nocardia* include imipenem, amikacin, and third-generation cephalosporins (ceftriaxone and cefotaxime). Minocycline, dapsone, and extended-spectrum fluoroquinolones are also known to have in vitro and/or in vivo activity against *Nocardia*.[6]

Because antibiotic susceptibility among *Nocardia* species and isolates varies, severe infections, including CNS disease, are generally treated with TMP-SMX, plus one or occasionally two additional intravenous antibiotics. Isolate sensitivities should be obtained, and antibiotics tailored accordingly. Intravenous therapy should continue until clinical improvement occurs, usually for a minimum of 6 weeks in immunocompromised hosts. After intravenous induction, the patient may be switched to an oral maintenance regimen with TMP-SMX, minocycline, or amoxicillin-clavulanate, again depending on isolate susceptibilities.

The duration of therapy has not been rigorously studied; however, the relapsing nature of *Nocardia* infections has led most experts to conclude that CNS disease in an immunosuppressed host requires a minimum of one year of treatment,[3] and lifelong suppressive therapy may be considered.

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## A Construction Worker with Headache and Visual Loss

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### Case Presentation

A 34-year-old man presented to an ophthalmologist with progressive visual blurring and headache over the month prior to evaluation. He was originally from rural Ecuador, and had been working in construction in New York for ten years. His friends noted that he had been having spells during which he would be unresponsive for several seconds. On physical examination, the patient was found to have bilateral papilledema (Figure **3d.1**), and his visual acuity was only light perception bilaterally. He was referred emergently to the emergency department for evaluation of increased intracranial pressure. Imaging of the brain revealed dilated ventricles, multiple calcified lesions, and multiple fluid-filled cysts in the brain parenchyma. At the base of the brain, clusters of cysts (racemose disease) were obstructing the fourth ventricle (Figures **3d.2**–**3d.4**).

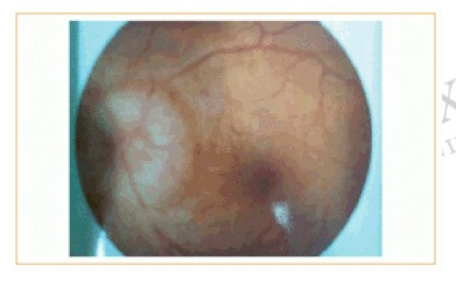





Figure 3d.1
Fundoscopic examination revealing papilledema.



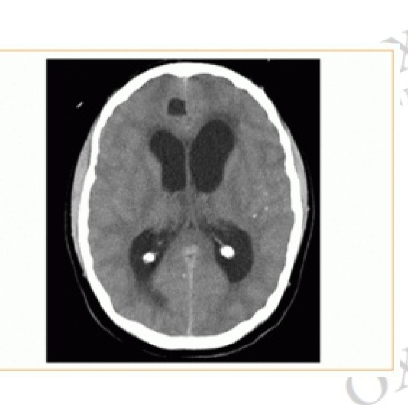






Figure 3d.2
Head CT, axial view revealing hydrocephalus, viable cysts, and calcifications.






Figure 3d.3
Brain MRI, sagittal view showing hydrocephalus and viable cysts in the frontal cortex and at the base of the brain.

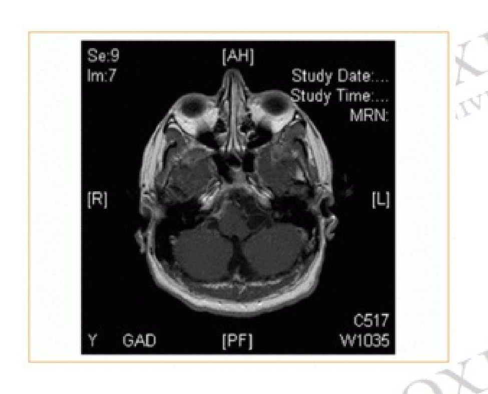



Figure 3d.4
Brain MRI, axial view revealing racemose lesions at the base of the brain obstructing CSF flow through the fourth ventricle.

An external ventricular drain was placed emergently to reduce the increased intracranial pressure. Some of the ventricular cysts were so closely adherent to the midbrain that they could not be removed, and a ventriculoperitoneal shunt was placed. The patient was treated with steroids and prolonged courses of high-dose albendazole, but the racemose disease was unrelenting. He was subsequently admitted with multiple ventriculoperitoneal shunt malfunctions and infections, and died within 12 months of his initial presentation.

**Case 3d Discussion: Neurocysticercosis**

## Epidemiology and Clinical Presentation

Neurocysticercosis is an important disease mainly endemic to developing nations where pigs and humans live in close contact. It is the leading cause of adult-onset seizures in the developing world, and in some rural communities in South America, 20% of the population have asymptomatic cysts on neuroimaging.[1] The etiologic agent of neurocysticercosis is the larval form of the tapeworm *Taenia solium*. This helminth is responsible for two very distinct clinical syndromes. The most benign of these syndromes, intestinal human taeniasis, develops after the ingestion of live cysticerci (tissue cysts) in undercooked pork, followed by attachment of the scolex (anterior end of the worm) to the human intestinal wall. The intestinal tapeworm then slowly elongates over time, as proglottid segments are added in a process called *strobilization*. Adult tapeworms are visible to the naked eye, and can reach several meters in length. The egg-filled proglottid segments are shed in human stool; when the segments are ingested by pigs, oncospheres penetrate the intestinal wall, disseminate throughout the pig's tissues and become encysted, and the lifecycle continues (Figure **3d.5**).

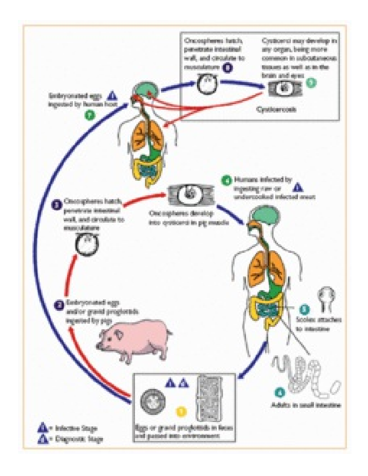








Figure 3d.5
Lifecycle of *Taenia solium*.

*Source*: Centers for Disease Control and Prevention http://www.dpd.cdc.gov/dpdx

In contrast, neurocysticercosis develops when humans accidentally ingest eggs via contamination of food or water with stool shed by a human infected with the adult worm. The

oncospheres penetrate the human intestinal wall, disseminating throughout human tissue and becoming encysted. The most dreaded complications of this event are when the organisms reach the central nervous system. Dozens of cysts may lodge in the brain or ventricles and evade immune detection for years. Once the parasites are lodged in the brain parenchyma, they form cysticerci that undergo four stages of involution. The vesicular stage is characterized by a cyst with translucent vesicular wall, transparent fluid, and a viable invaginated scolex. The cyst then develops a thick vesicular wall, the fluid becomes turbid, and the scolex degenerates during the next stage, which is termed the *colloidal stage*. An intense inflammatory host response is seen, and is reflected histologically by varying degrees of acute and chronic inflammation. The cyst continues to degenerate as it moves into the granular stage, which is characterized by a thick vesicular wall, degenerated scolex, gliosis, and little inflammatory host response. Ultimately, the parasite transforms into coarse calcified nodules—the *calcific stage*. As they degenerate, an inflammatory response is elicited that may cause headaches, nausea, and seizures. The intraventricular and subarachnoid (cisternal) forms of neurocysticercosis are seen in 15% to 54% of patients, and present clinically in a more aggressive manner as compared to the parenchymatous form. Patients commonly present with raised intracranial pressure caused by large cyst size or load, occlusion of CSF pathways, associated ependymitis, and basal arachnoiditis. The racemose form of neurocysticercosis is characterized by the presence of a cluster of large cisternal cysts that resemble a “bunch of grapes.”[1]

## Diagnosis

Diagnosis of the presence of an intestinal tapeworm may be achieved by examination of the stool for the presence of *T. solium* eggs or proglottids, but stool studies are usually not useful in the diagnosis of neurocysticercosis. Neuroimaging is the most common diagnostic modality for the larval form of the disease. Early in the infection, a vesicular cyst appears as a spherical lesion on computerized tomography (CT) and as a CSF-like signal on magnetic resonance imaging (MRI); both modalities may reveal the invaginated scolex. In the degenerative phase, the cyst has a ring-like appearance, or nodular contrast enhancement, with or without perilesional edema. The final stage is observed when the cyst dies and a process of mineralization and resorption takes place, resulting in a calcified nodule. While CT is generally adequate to detect the presence of most cysts, MRI may reveal cysts not seen on CT, particularly in the anatomic structures of the posterior fossa. Serologic testing via enzyme-linked immunoelectrotransfer blot assay (ETIB) has a sensitivity and specificity approaching 100% for patients with two or more cystic or enhancing lesions. The test performance declines for patients with single intracranial lesions or calcified lesions, in which a sensitivity as low as 50% has been reported. In cases in which the cyst is surgically removed, microscopic examination may reveal the typical undulating membrane pattern of *Cysticercus cellulosae*, the pathologic description of the larval form of *Taenia solium* (Figure **3d.6**).

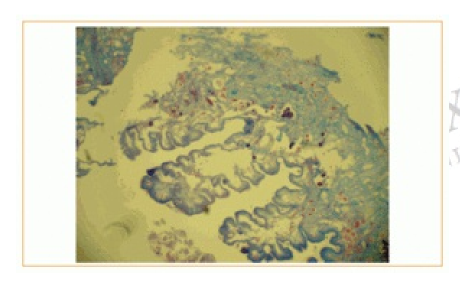




Figure 3d.6
Brain biopsy revealing undulating membrane of *Cysticercus cellulosae*. Original magnification 40x. Image courtesy of George Kleinman.

## Management

Treatment of neurocysticercosis is controversial, in part because the natural history of the disease is for the cysts to slowly involute over time. Many patients with less than five cysts can be managed with antiepileptic medications alone. In the presence of 5–100 cysts, consensus guidelines support the use of antiparasitic medications in order to decrease the likelihood of further seizures. Praziquantel is effective against the adult tapeworm; however, albendazole achieves superior levels in the central nervous system (particularly when given concomitantly with corticosteroids), and is therefore considered the first-line agent. In patients with numerous cysts, antiparasitic therapy is often combined with corticosteroids in order to prevent the sudden encephalitis that may result from the inflammatory response to the parasitic antigens.[2] Antiparasitic treatment is not currently recommended for patients with nonviable lesions; however, patients with calcified lesions might have intermittent perilesional edema and present with seizures, requiring antiepileptic medications.

Intraventricular cysts may not respond to medical management, and often require surgical removal if they are obstructing the flow of CSF. Neuroendoscopic removal is a preferred method, since it is less invasive than open neurosurgery. Unfortunately, patients may have cysts that cannot be removed surgically, and may require ventriculoperitoneal shunt placement to relieve increased intracranial pressure. These shunts are prone to malfunction and bacterial infection due to the accumulation of parasite antigens and inflammatory proteins. Racemose neurocysticercosis is a form that is often refractory to therapies, though some investigators have had success with higher doses of albendazole and steroids for prolonged periods of time.[3]

Prevention of the disease requires improved sanitation in developing countries, but public health campaigns have employed multiple strategies for control of the disease. Education campaigns have highlighted proper cooking of pork, as well as recognition of infected tissue by butchers and food handlers. Mass treatment campaigns focusing on both pigs and humans have also been employed in efforts to eradicate the disease in communities with high endemicity. A porcine vaccine is currently available, but current strategies have only been successful in partially limiting transmission of the infection.[4]

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 42-Year-Old Man with Progressive Cognitive Decline

**Chapter:** A 42-Year-Old Man with Progressive Cognitive Decline
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0014

### Presentation and Case History

A 42-year-old man with a history of sarcoidosis was admitted for elective hip arthroplasty due to osteoarthritis. In the postoperative period he was found to be confused and agitated, and further investigation revealed that he had been having cognitive problems for several months. His roommate noted that he was having memory lapses, as well as personality changes. He had been working as an actor and dancer, but was finding it increasingly difficult to perform even the basic activities of daily living. The patient had been diagnosed with severe pulmonary sarcoidosis three years prior to presentation, but had not been receiving any immunosuppressive medications.

On physical examination, he was afebrile and his other vitals signs were unremarkable. His neurological exam was notable for disorientation to the time of year, left-sided neglect, horizontal nystagmus, and abnormal cerebellar function with dysmetria on the left. Further examination revealed bilateral lower extremity weakness and hyporeflexia. MRI of the brain revealed scattered white matter lesions in both cerebral hemispheres, the largest of which were in the left frontal parietal lobe and the left frontal lobe. No contrast enhancement or mass effect was noted (Figures **3e.1** and **3e.2**).

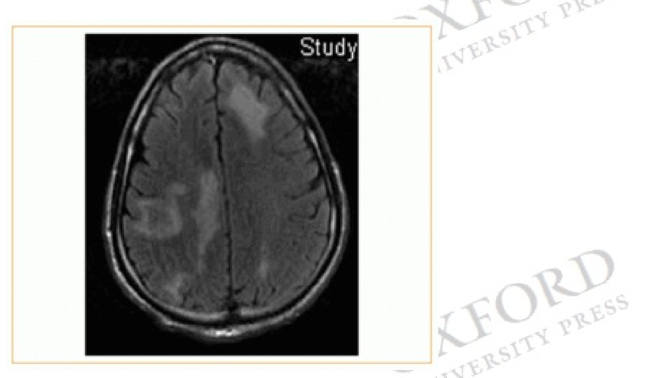



Figure 3e.1


Brain MRI, axial view revealing scattered white matter lesions in both cerebral hemispheres, the largest of which were in the left frontal parietal lobe and the left frontal lobe.

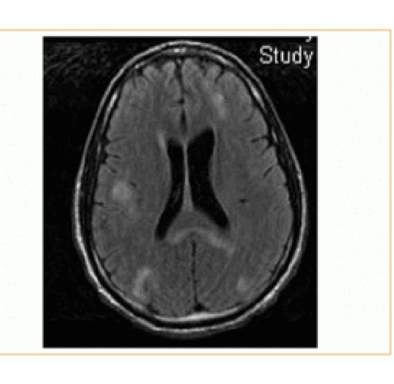





Figure 3e.2
Brain MRI, axial view revealing scattered white matter lesions in both cerebral hemispheres, the largest of which were in the left frontal parietal lobe and the left frontal lobe.

His laboratory evaluation included normal erythrocyte sedimentation rate and C-reactive protein, and negative human immunodeficiency virus ELISA, tuberculosis skin test, rapid plasma reagin, Lyme antibody, Toxoplasma antibodies, and autoimmune studies. Brain biopsy revealed multiple areas of selective demyelination at various stages of evolution within the cerebral white matter. The oligodendrocytes (i.e., myelin-producing cells) had large nuclei and intranuclear basophilic material, and the astrocytes were enlarged and had irregular nuclei (Figures **3e.3** and **3e.4**). The patient's cerebrospinal fluid JC virus PCR was positive. Based on the history, brain biopsy, and laboratory evidence, the patient was diagnosed with progressive multifocal leukoencephalopathy (PML), and was treated with supportive management including physical therapy.

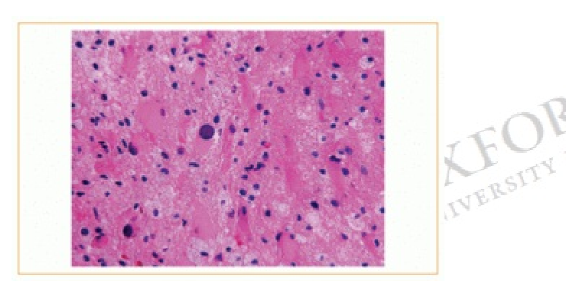




Figure 3e.3
Brain biopsy revealed multiple areas of selective demyelination at various stages of evolution within the cerebral white matter. The oligodendrocytes had large nuclei and intranuclear basophilic material and the astrocytes were enlarged and had irregular nuclei. Image courtesy of George Kleinman.



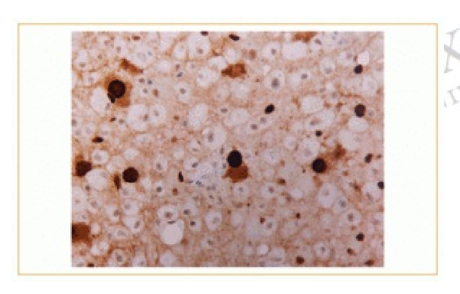


Figure 3e.4
Brain biopsy with immunohistochemical stain for SV40 (which cross reacts with JC virus) revealed multiple infected cells. Image courtesy of George Kleinman.

**Case 3e Discussion: Progressive Multifocal Leukoencephalopathy**

## Clinical Presentation and Diagnosis

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease associated with reactivation or primary infection of JC virus in the central nervous system of immunosuppressed individuals. PML was first described as a clinical entity in 1958, in patients with hematologic malignancies, but the epidemiology of PML changed with the emergence of AIDS. Prior to the 1980s, PML was described in patients mainly with lymphoproliferative and myeloproliferative diseases, but was also observed in patients with cell-mediated immune defects, those treated with corticosteroids and, rarely, in patients without apparent immunocompromise. During the onset of the AIDS epidemic, 1%–4% of HIV-positive patients had PML, and half of the deaths from PML occurred in patients with AIDS. PML has also emerged as an important complication in patients taking immunosuppressant medications for organ transplantation, or monoclonal antibody anti-inflammatory medications such as natalizumab, rituximab, and efalizumab.[1] Cases of PML in pulmonary sarcoidosis are rare, but severe cases have been described even in the absence of immunosuppressive medications.[2]

JC virus is a polyomavirus that was first isolated from brain tissue in a patient with PML in 1971. Asymptomatic infection with the JC virus likely occurs during childhood and persists for years without clinical consequences in most immunocompetent patients. Viral transmission is thought to occur through inhalation or close contact, and viral reservoirs for latent disease include the kidneys, central nervous system, and tonsils. In PML, JC virus infects astrocytes and oligodendrocytes and leads to decreased myelin production. The role of the 5HT2a serotonin receptor as a cellular receptor for JC virus has led to investigation of potential therapeutic benefits of serotonin receptor antagonists, such as mirtazapine. It remains unknown whether PML results primarily from primary infection, reactivation of a latent infection of the brain, or a secondary infection of the brain due to viremia originating from a latent infection of the kidney. Latent infections of both brain and kidney have been demonstrated by JC virus polymerase chain reaction (PCR) of renal and cerebral tissue, as well as urine and cerebrospinal fluid (CSF) PCR of asymptomatic individuals.

PML presents with subacute to rapidly progressing neurological deficits, including hemiparesis, cognitive deficits, ataxia, visual field deficits, cranial nerve involvement, and seizures. Severe manifestations and symptoms late in the course of disease include quadriplegia, blindness, dementia, and coma. Clinical deterioration and death usually take place within 6 months of diagnosis, and the median survival is 3 months. Disease typically involves cerebral white matter, but it can include the cerebellum and brainstem. Remyelination of damaged areas does not usually occur in HIV-positive PML patients treated with antiretroviral therapy (ARVs), and over 80% of those who survive this fatal disease have severe neurologic deficits.[3]

The differential diagnosis for PML includes HIV encephalopathy, primary central nervous system lymphoma, stroke, and brain tumor. The gold standard for diagnosis for PML is a brain biopsy demonstrating features of JC virus infection. Pathologic characteristics of PML include cerebral white matter with asymmetrical foci of demyelination, and different stages of evolution of demyelination. Electron microscopy may reveal polyomavirus in enlarged oligodendrocytes. A positive JC virus CSF PCR supports a diagnosis of PML when the patient is presenting with consistent clinical and radiologic features, but a negative PCR does not exclude disease. Sensitivities of CSF PCR range from 72%–92%, and specificity ranges from 92%–100%.[1] There is inconclusive evidence regarding the use of quantification of JC viral DNA PCR as a prognostic marker. CSF cell count, glucose, and protein are typically normal. Brain imaging reveals symmetric or asymmetric multifocal areas of white matter demyelination. On computed topography (CT) scans, PML lesions are hypodense and scattered throughout the parenchyma, and are not characterized by edema or contrast enhancement. On magnetic resonance imaging (MRI), lesions have an increased signal on T2-weighted images. Electroencephalography (EEG) can reveal focal slowing, but may be normal.[1]

## Management

Most patients in whom JC virus is detected are asymptomatic, and treatment is not necessary. There is currently no proven treatment regimen for non-HIV-associated PML, and existing studies largely involve HIV-positive patients. The Aids Clinical Trials Group (ACTG) performed a multicenter, randomized study comparing the efficacy of antiretroviral treatment alone versus antiretroviral treatment with the addition of intravenous or intrathecal cytarabine in biopsy-proven, HIV-infected PML patients. There was no efficacy or survival benefit in the intervention group, and those treated with cytarabine developed thrombocytopenia and anemia more often than the control arm.[4] Other medications that have been studied include interleukin-2, cidofovir, and interferon alpha-2, but no convincing data exists to support their use. In HIV-positive patients there is a definite role for antiretroviral (ARV) therapy, and median survival is now 1.8 years versus 0.4 years during the pre-ARV era.[3] Immune reconstitution inflammatory syndrome (IRIS) may occur after treatment initiation.

In the case of organ transplantation, possible benefit with reduction in immunosuppression has been documented through case reports.[5] One study with HIV-negative PML patients with hematologic malignancies, rheumatologic diseases, and transplantation showed a benefit of intravenous cytarabine, 2 mg/kg every 12 hours for 5 days, in stabilizing neurologic function in 7 out of 19 (36%) patients on 2.5 year follow-up; however, patients experienced bone marrow toxicity.[6] Cidofovir is not recommended for PML as per the American guidelines for the treatment of AIDS-associated PML. In vitro studies have demonstrated effectiveness of mirtazapine; it is postulated that JC virus uses serotonin receptors for cell entry. A case report describes a woman with polycythemia vera and PML to have radiographic and clinical improvement within a month of treatment with mirtazapine.[7] Mefloquine has in vitro effects on JC virus, and is currently under investigation.

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## A 23-Year-Old Contact Lens Wearer with Eye Pain and Decreased Vision

**Chapter:** A 23-Year-Old Contact Lens Wearer with Eye Pain and Decreased Vision
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 23-year-old woman presented with a 2-day history of right eye pain, redness, and decreased vision. At presentation, the patient was wearing 2-week disposable soft lenses for myopic correction. The patient wore her contact lenses daily, averaging 12 to 14 hours per day, and occasionally slept in her lenses. Prior to the onset of symptoms, the patient had worn her contacts continuously for 48 hours. The patient occasionally showered without removing her lenses, but denied wearing the lenses in hot tubs or swimming pools. She stored her contact lenses with over-the-counter multipurpose contact lens solution.

On examination, uncorrected visual acuity was 20/400 in the right eye, no improvement with pinhole, and 20/40 in the left eye improving to 20/20 with pinhole. There was moderate edema of the right eyelids with visible epiphora. Slitlamp examination of the right eye showed diffuse conjunctival injection, chemosis, and a paracentral corneal ulcer with epithelial staining measuring 2.5mm × 2.0mm (Figure **4a.1**). The ulcer showed severe dense suppurative stromal infiltrate, approximately one-third of the corneal thickness. Uninvolved portions of the cornea had a diffuse ground-glass appearance secondary to edema. Anterior chamber reaction of 1+ cell was noted with no hypopyon present. Examination of the left eye was unremarkable.

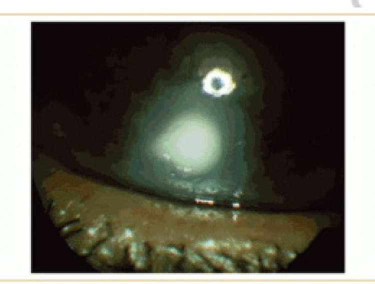


Figure 4a.1
Paracentral corneal ulcer with dense suppurative stromal infiltrate and surrounding edema.

The contact lens case and corneal scrapings were taken for Gram stain and culture. Treatment was initiated with broad-spectrum fortified antibiotics consisting of tobramycin (15mg/ml) and cefazolin (50mg/ml) every one hour while awake, along with cyclopentolate hydrochloride 1% three times daily for patient comfort. Contact lens use was discontinued. After initiating treatment, the patient was followed closely as an outpatient on a daily basis. The size of the epithelial defect decreased over the first 24–48 hours of treatment, and completely healed in approximately one week. The stromal infiltrate was slower to resolve, fading over the course of 3 to 4 weeks.

The cultures returned positive for *Pseudomonas aeruginosa,* susceptible to tobramycin. Cefazolin was discontinued and the patient was maintained on fortified tobramycin, with reduction in the frequency of administration as correlated with clinical improvement. Final uncorrected visual outcome was 20/60 in the right eye, improving to 20/30 with pinhole, and unchanged in the left eye.

#### Case 4a Discussion: *Pseudomonas* Keratitis

Clinical Features and Diagnosis

Bacterial keratitis is a common sight-threatening ophthalmic infection. These infections are generally rapid in both onset and progression, and if left untreated can lead to corneal destruction with perforation and potential loss of the eye. Disruption of corneal epithelial integrity, secondary to multiple etiologies, is a common risk factor for infectious keratitis. In developed countries, the most common risk factor is contact lens wear.[1] Other risk factors include trauma, history of keratopathy, contaminated ocular medication or contact lens solution, and impaired host defense secondary to malnutrition, alcoholism, diabetes, or HIV.

Among contact lens wearers, increased risk for infectious keratitis is most commonly due to noncompliance with proper lens-care protocol.[2] Deviations from protocol include overnight lens use, which conveys greater risk with increased number of nights, poor hygiene, and improper cleaning and storage of lenses. Important questions to ask a contact lens wearer include type of contact lens (soft, hard, rigid gas permeable), schedule of wear (daily, extended, hours per day, overnight wear), disposable interval, cleaning and storage routine (type of cleaning solution, tap water use), and activities while wearing lenses (swimming, showering, use of hot tub).

The ocular surface has a number of natural defenses against infection. The eyelids and lashes act as a physical barrier to foreign material. Each blink pumps tears from the lacrimal gland and distributes the tear film across the cornea, while sweeping away microorganisms. The tear film itself contains many features, such as lysozyme, lactoferrin, ceruloplasmin, immunoglobulins, and complement factors that inhibit microbial growth.[1] An intact corneal epithelium not only acts as a mechanical barrier against microbial entry, but also actively phagocytizes microbes for removal.

Contact lenses increase the risk of infectious keratitis by adversely affecting these natural defenses.[3] The lenses act as a scaffold for microbial growth, while interfering with the sweep of the eyelids and tear flow across the cornea. Insertion and removal of the lenses, as well as lens defects, may cause trauma with epithelial damage allowing microbial entry. The normal cornea receives its oxygen by diffusion from the air. Contact lenses interfere with this process and induce corneal hypoxia, which leads to reduced epithelial turnover and compromised cellular junctional integrity, and greater epithelial fragility.

Most patients with infectious keratitis will present with acute onset of eye pain, conjunctival injection, and decreased visual acuity.[4] The history in a person suspected of bacterial keratitis should include the ocular symptoms (visual acuity changes, pain, characteristics of discharge, photophobia, onset, duration), past ocular history (trauma, prior eye surgery, past infections, use of contact lenses), current use of any ocular medication, and other systemic medical problems. Baseline visual acuity and slit lamp examinations are also essential. The eyelids are examined for any ulcerations, glandular dysfunctions, or eyelash abnormalities. The conjunctiva is inspected for any injection or chemosis, follicular or papillary changes, and discharge. The cornea may show an epithelial defect with fluorescein staining, a stromal infiltrate, ulceration, thinning, or frank perforation. The size, depth, margin, and location of any infiltrate are important in the diagnosis and management of the patient. Patients with infiltrates suspected of being vision-threatening may require hospitalization for treatment. Keratitis may also be associated with anterior chamber inflammation and hypopyon.

*Pseudomonas keratitis* is noted for being rapidly progressive, and is frequently associated with a dense ring-like stromal infiltrate and marked suppuration that may very quickly lead to corneal necrosis and perforation. However, although a careful history and exam may provide clues to the final diagnosis, there are no specific signs or symptoms that are pathognomonic for the causative agent. Cultures are necessary for definitive diagnosis of the infectious etiology. The most common organisms in bacterial keratitis are those normally part of the ocular flora.[3] These include *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus* species, and *Pseudomonas aeruginosa*. Among patients with contact lenses, the most common causative organism is *Pseudomonas aeruginosa*. In addition, though the most common type of infectious keratitis in contact lens wearers are bacterial, other etiologies such as fungal keratitis and *Acanthamoeba* keratitis must be included in the differential for this high-risk group.

## Treatment

Treatment is usually initiated with intensive broad-spectrum topical antibiotics applied frequently (every 30–60 min) around the clock, targeting the most common causative organisms.[4] Patients who cannot comply with the dosing regimen or have vision-threatening infections may require hospitalization for treatment. The initial choice of antibiotics may include a fluoroquinolone, such as ciprofloxacin, possibly combined with other fortified antibiotics (tobramycin, gentamicin, cefazolin, vancomycin, etc.). Those patients treated on an outpatient basis must be followed closely with daily exams until the condition clinically improves. The antibiotics are modified according to the culture and susceptibility results, while the frequency of dosing may be tapered with clinical improvement. A worsening clinical picture despite appropriate treatment should prompt reculturing and consideration of other, less common causative agents.[3] Additional therapy for other sources of infection, such as fungus or *Acanthamoeba,* should be considered. The prognosis and ultimate visual out come varies markedly, depending on the causative organism in addition to the size and location of the lesion.

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## A 46-Year-Old Man with a Painful Red Eye and a Rash

**Chapter:** A 46-Year-Old Man with a Painful Red Eye and a Rash
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 46-year-old Hispanic man presented with a 2-day history of a red, painful right eye associated with a decrease in vision. The patient also complained of floaters and a nonpruritic facial rash that he had noticed two weeks before presentation. He had no known past medical history and was taking no medications. On physical examination, he was afebrile but had a maculopapular rash on the face, palms, and soles. Ophthalmic examination revealed a vision of counting fingers in the right eye, and 20/20 in the left. The right eye had conjunctival injection and on slit lamp examination, both anterior chamber inflammation and posterior synechiae were seen (Figure **4b.1**). Dilated fundoscopic examination was significant for a 3+ vitritis (Figure **4b.2**), associated with multiple active placoid chorioretinal lesions in the mid-periphery (Figure **4b.3**).

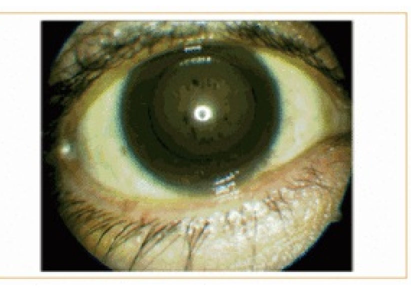




Figure 4b.1
Right eye with conjunctival injection. On slit-lamp examination both anterior chamber inflammation and posterior synechiae were seen.

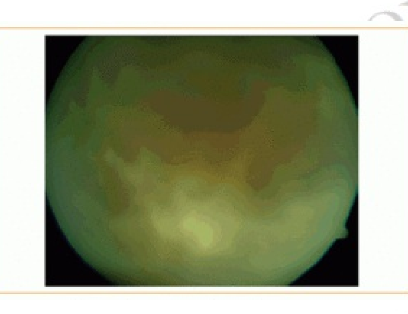




Figure 4b.2
Dilated fundoscopic examination was significant for a 3+ vitritis.

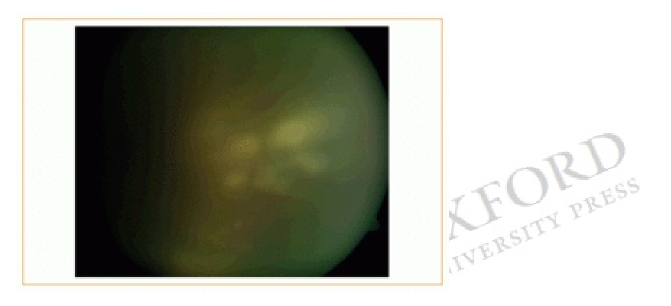


Figure 4b.3
Dilated fundoscopic examination with multiple active placoid chorioretinal lesions in the mid-periphery.

The patient was diagnosed with a panuveitis, and additional testing included chest radiography, tuberculin skin testing, and serologic testing for syphilis (RPR-FTA). The differential diagnosis for this patient included tuberculosis, syphilis, viral retinitis (CMV, acute retinal necrosis), sarcoidosis, toxoplasmosis, and lymphoma; however, the constellation of both systemic and ocular signs and symptoms was highly suggestive of syphilis. Syphilis RPR and IgG were both reactive, and the serum titer was found to be 1:4096. A lumbar puncture was performed, and the cerebrospinal fluid RPR was 1:512. The patient was diagnosed with neurosyphilis and admitted for treatment with 14 days of intravenous penicillin, as well as topical corticosteroids and cycloplegics. At this time, the patient was found to have advanced AIDS with positive HIV serology and a $CD4^{+}$ lymphocyte count of 46 cells/µl.

Clinically, the patient's condition improved rapidly: within two weeks, the vision in the right eye had improved to 20/100, with partial resolution of anterior and vitreous inflammation (Figure **4b.4**). Over time, the lesions were slowly resolving, decreasing in both size and activity (Figure **4b.5**) until they left a hyperpigmented chorioretinal scar (Figure **4b.6**). At six months, serologies continued to be positive at 1:256, and one year after diagnosis, the ratio was 1:128. Repeat lumbar punctures were declined by the patient, but after resolution of the panuveitis, the patient initiated antiretroviral medications.



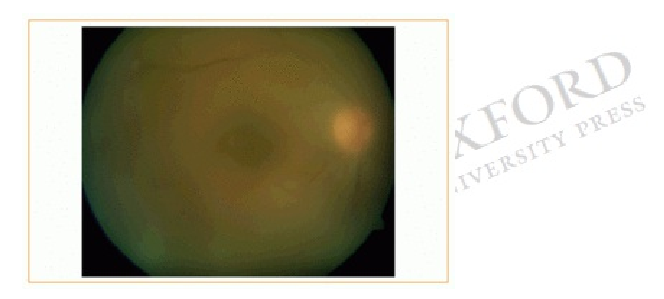


Figure 4b.4
Dilated fundoscopic examination showing partial resolution of anterior and vitreous inflammation.

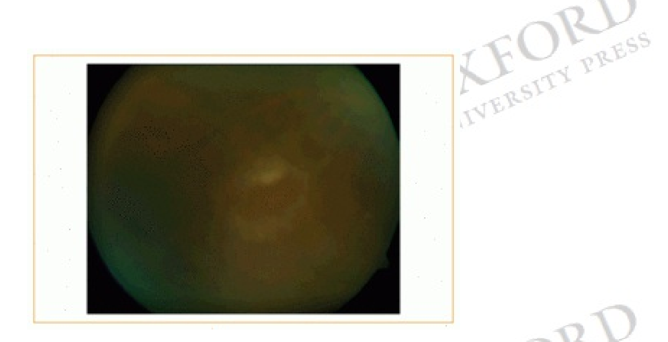


Figure 4b.5
Dilated fundoscopic examination showing lesions were slowly resolving, decreasing in both size and activity.



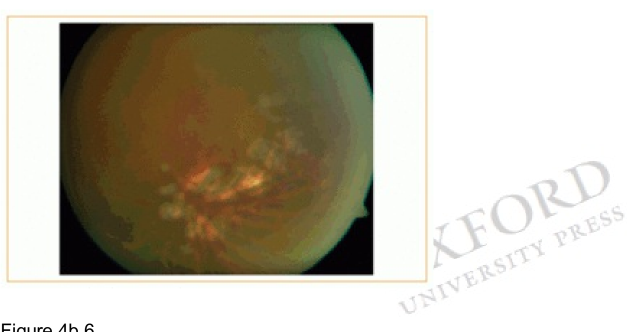




Figure 4b.6
Dilated fundoscopic examination showing a hyperpigmented chorioretinal scar.

**Case 4b Discussion: *Treponema pallidum* Uveitis**

## Uvea Anatomy

The uvea is the middle coat of the eye that begins anteriorly as the iris and ciliary body, and extends posteriorly to include the choroid. Inflammation of the anterior uveal tract is called anterior uveitis (i.e., iritis, iridocyclitis). Inflammation of the posterior segment is differentiated based on the site of active inflammation (e.g., choroiditis, vitritis, pars planitis, retinitis, chorioretinitis). The presentation of a patient with uveitis depends on the portion of the uveal tract that is involved. Anterior uveitis usually produces photosensitivity and redness. Patients presenting with posterior or intermediate uveitis (vitritis) are less likely to experience pain, but may experience visual changes such as floaters or reduced visual acuity.

## Clinical Features

Syphilis is a sexually transmitted, chronic, systemic infection caused by the spirochete *Treponema pallidum*. If left untreated, the disease progresses though four stages and may cause significant pathology in any major organ of the body. From 2000 to 2004, the number of cases of primary and secondary syphilis in the US increased from 5,979 to 7,980, and the rate increased from 2.1 to 2.7 cases per 100,000. The increase was seen primarily as a result of rising rates among men who have sex with men.[1]

Syphilis is known as the "great masquerader." Involvement of the eye may be the presenting manifestation of syphilis, and is often associated with delayed diagnosis and delayed treatment, which may result in irreversible visual loss and structural damage. The eyes are affected in approximately 10% of cases, and the most common presentation of syphilis in the eye is uveitis.[2] Other ocular manifestations include interstitial keratitis, scleritis, retinal vasculitis, neuroretinitis, and cranial and optic neuropathies. The Argyll Robertson pupil is most commonly seen late in the disease, although it can present early.[3] The pupils are unequal, irregular, and miotic, with a light-near dissociation.

The characteristics of syphilitic iridocyclitis and chorioretinitis are not pathognomonic of the disease, and other etiologies should be entertained. Typically, chorioretinitis manifests as multiple elevated creamy white lesions with an associated vitritis. Placoid chorioretinitis (geographic flat creamy white lesions) of the macula are characteristic in patients with con-current HIV infection.[4] Syphilitic uveitis can occur as soon as 6 weeks after primary infection, but may not manifest for many years. HIV and syphilis are defined as coinfections, often acquired simultaneously, and a diagnosis of syphilitic uveitis should prompt HIV testing. Ocular syphilis is not an ophthalmic opportunistic infection; however, when diagnosed concurrently, treatment of the syphilis is indicated before initiation of antiretroviral therapy, to decrease the likelihood of the immune reconstitution syndrome.

## Diagnosis

Uveitis can be divided into two broad categories: infectious and noninfectious. The differential diagnosis of syphilitic uveitis includes tuberculosis, Lyme disease, herpetic disease, toxoplasmosis, sarcoidosis, Vogt-Koyanagi-Harada disease, white dot syndromes, and Wegner's granulomatosis among others. Since it is nearly impossible to rule out syphilis as a cause of uveitis based solely on clinical presentation, the evaluation of any unexplained ocular inflammation should include testing for syphilis.[2] Diagnosis demands a high level of clinical suspicion, and includes both treponemal-specific and nontreponemal serologic tests.

There are two general categories of serologic tests: (1) nontreponemal tests, such as the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR), and (2) treponemal tests, such as the fluorescent treponemal antibody absorbed (FTA-ABS).[5] There are several shortcomings to these serologic tests, as several comorbidities can lead to false negative and false positive testing. For example, HIV infection can lead to a false negative result in both the nontreponemal and treponemal tests,[5] and highlights the need for a high clinical suspicion when diagnosing syphilitic uveitis.

When serological test results are positive, the possibility of neurosyphilis should be investigated by means of lumbar puncture and study of the relevant antibody markers in cerebrospinal fluid (CSF). A positive CSF VDRL is considered diagnostic for neurosyphilis; however, VDRL may be nonreactive in some cases of active neurosyphilis. CSF FTA-ABS is less specific, but is highly sensitive and is used to exclude neurosyphilis, though some clinicians consider syphilitic uveitis to be equivalent to the diagnosis of neurosyphilis for the purposes of treatment.[5]

## Treatment

Conventional syphilis staging is of little use in understanding ocular syphilis;[6] once diagnosed with syphilitic uveitis, patients should be treated with intravenous penicillin for 10–14 days. Topical, periocular, and systemic corticosteroids also have roles in the management of the ocular sequelae of syphilis. Topical corticosteroids can minimize the inflammatory damage of interstitial keratitis and anterior uveitis. Oral and IV corticosteroids can be used for posterior uveitis, scleritis, and optic neuritis; however, only timely treatment with systemic penicillin can lead to resolution of ocular inflammation.

There are no proven alternatives to penicillin in the treatment of neurosyphilis. The CDC also recommends that penicillin be used for the treatment of all stages of syphilis in patients coinfected with HIV. Therefore, penicillinallergic patients in those categories should be desensitized and treated with penicillin.[1] Early treatment is the key to reducing ophthalmic structural damage from a syphilitic infection. These anatomic complications include posterior synechiae, secondary glaucoma, cataract, retinal scarring, macular edema, and retinal detachment that may ultimately compromise vision.

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

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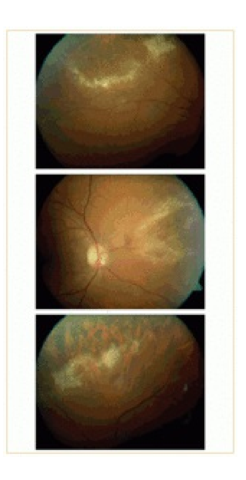
## Cytomegalovirus Retinitis in a Patient with AIDS

**Chapter:** Cytomegalovirus Retinitis in a Patient with AIDS
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0017

### Case Presentation

A 41-year-old Hispanic female with a history of HIV and cytomegalovirus retinitis (CMVR) was referred to an ophthalmology service for management. The patient was diagnosed with bilateral CMVR one year prior, and had been treated successfully with induction and maintenance ganciclovir. Although she was prescribed antiretrovirals, the patient's CD4+ cell count remained low ((50 cells/μl), and she developed a recurrence of the CMVR sixth months later. She was again treated with induction dose intravenous ganciclovir, but her disease continued to progress and ganciclovir resistance was suspected. CMV resistance testing revealed mutations at both UL-97 and UL-54 loci, implying an absolute resistance to ganciclovir, and the patient was treated with induction dose foscarnet. Although the CMVR responded, the patient developed acute renal failure from the foscarnet, and the medication was discontinued. The patient was then referred to our service for consultation.

On examination, the vision was measured at 20/70 in the right eye and 20/40 in the left eye. Slit lamp examination was noteworthy for fine pigmented keratic precipitates on the corneal endothelium in both eyes. Dilated fundoscopic examination revealed areas of active CMVR in both eyes (Figures **4c.1 to 4c.5**).







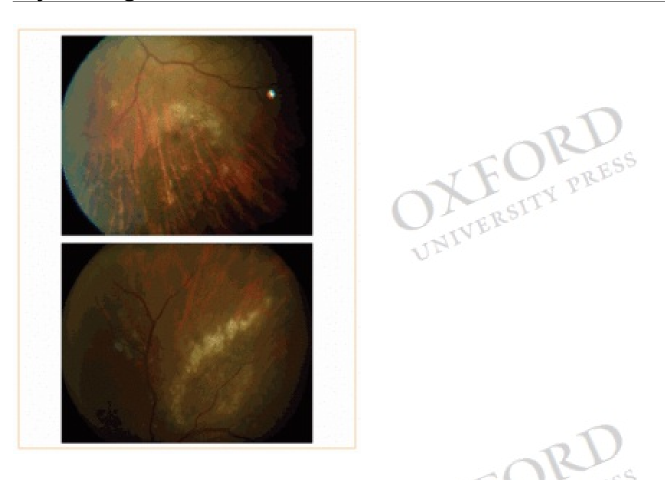



Figure 4c.1 through 4c.5
Dilated fundoscopic examination revealed areas of active CMVR in both eyes.

Given the ganciclovir resistance and adverse effects of foscarnet (implying intolerance to cidofovir as well), the patient was treated with intravitreal injections of foscarnet, first on a biweekly basis as induction. The patient was noted to clinically improve (Figures **4c.6 to 4c.9**), and after the CMVR became inactive (Figures **4c.10 to 4c.12**), the intravitreal treatment continued at a weekly interval for maintenance therapy. After 6 months of this regimen, and a change to the antiretroviral medications, the patient's CD4+ cell count increased to 348 cells/μL over several months. At this point, intravitreal therapy was terminated and the CMVR has remained quiescent.



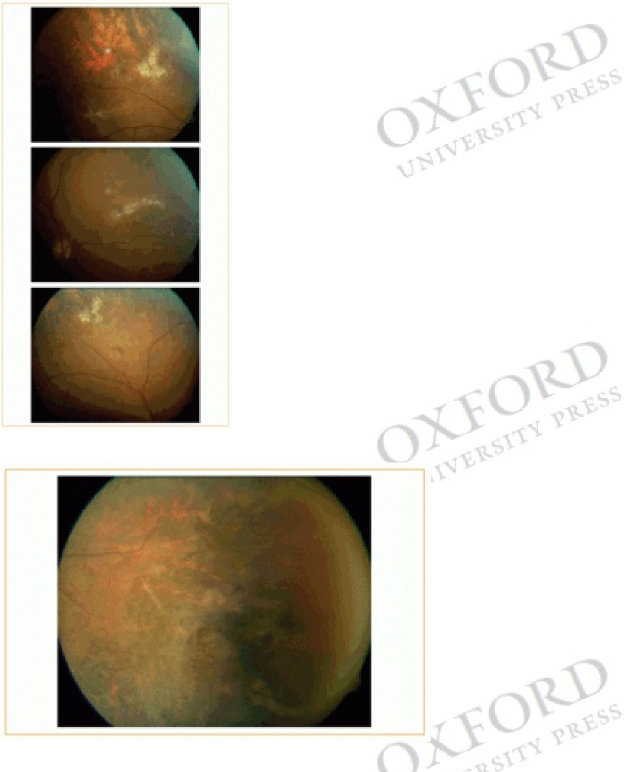
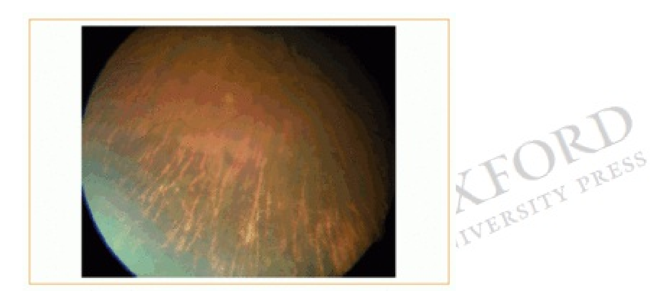









Figure 4c.6 through 4c.9
Dilated fundoscopic examination with clinically improved CMVR.





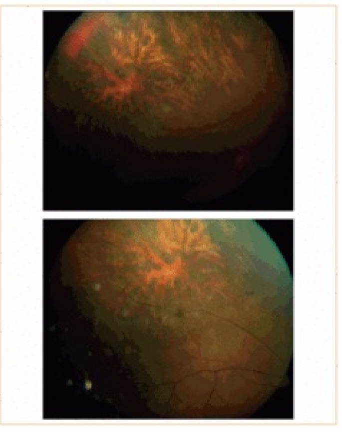




Figure 4c.10 through 4c.12
Dilated fundoscopic examination revealed inactive CMVR.

**Case 4c Discussion: Cytomegalovirus Retinitis**

## Clinical Features and Diagnosis

CMVR is caused by a ubiquitous DNA virus, found in up to 80% of the adult population. A member of the herpes family, it remains quiescent in the host until the host becomes immunocompromised, allowing for the reactivation and subsequent proliferation of the virus. The etiologies for an immune-compromised state include HIV/AIDS, transplant (both solid organ and bone marrow), and chemotherapy.[1] Although most commonly manifesting as a retinitis, CMV has been shown to cause meningitis, cerebritis, pneumonitis, and gastrointestinal disease including esophagitis, colitis, and hepatitis.

In patients with HIV/AIDS, CMVR is found mostly in patients with CD-4+ cell counts below 50cells/μl. With the advent of highly active antiretroviral therapy (HAART), there has been a 75%–80% decline in the incidence of CMV. In addition, rates of retinitis progression have decreased from 3.0 cases/patient year (PY) to 1.0 cases/PY in the HAART era.[2] Most new cases of CMVR appear to be in patients who are either HAART naïve, have HIV viruses with multiple resistance mutations, or are intolerant of their medications.[2, 3] HAART has also resulted in an improvement in the ability to control the retinitis and, subsequently, in the rates of complications. There is still a need for ongoing screening of patients with CD-4+ cell counts below 50cell/μl, and for ongoing monitoring of patients with inactive disease, as the disease can progress even in patients who have experienced immune recovery (CD-4+ )100). In addition, immune reconstituted patients may still experience significant visual loss, either secondary to factors such as foveal or optic nerve involvement, or chronic problems such as sequelae of immune reconstitution syndrome or cataract.

Patients with CMVR may present with either a decrease in vision or a complaint of floaters; however, some patients are entirely asymptomatic. On examination, the patient may have a slightly injected conjunctiva, fine keratic precipitates on the corneal endothelium, and a minimal anterior chamber reaction. There may also be cells in the vitreous. Fundus examination may reveal either single or multiple areas of infected retina adjacent to inactive, necrotic areas. This may be accompanied by blot hemorrhages and cotton wool spots (HIV retinopathy). Diagnosis is made on clinical examination by an experienced ophthalmologist.

## Treatment

Treatment consists of both systemic and local therapies. Systemic options include ganciclovir, valganciclovir, foscarnet, and cidafovir. All of these medications are virustatic, not virucidal, and are therefore administered as an induction dose until the disease is completely quiescent. The patient is then treated with chronic maintenance therapy. Ganciclovir, a nucleoside analogue of 2-deoxyguanosine, inhibits the replication of herpes viruses. Intravenous induction dose is 5mg/kg given twice daily, and maintenance is 5mg/kg daily (adjustment for renal function is necessary). The most common toxicity is bone marrow suppression. Resistance may develop when a mutation occurs at either the UL-97 or UL-54 loci of the CMV strain. Valganciclovir (Valcyte®) is an orally administered ganciclovir analogue, with similar bioavailability to ganciclovir. The induction dose is 900mg twice daily and maintenance is 900mg daily. Foscarnet is a pyrophosphate analogue, administered intravenously at 90mg/kg/bid during induction, with maintenance therapy at 90mg/kg/day. Foscarnet's most common toxicities include renal insufficiency and electrolyte imbalances. Cidofovir is a nucleotide analogue, and is dosed at 5mg/kg on a weekly basis as induction, and then given on an every 2–3 week maintenance schedule. Cidofovir can lead to severe, irreversible renal failure, and must be administered with probenecid both prior to, during, and after the infusion.

Local therapies have the advantage of delivering a high dose of medication directly to the affected area, with no systemic ramifications. Local therapies include intravitreal injections of either ganciclovir or foscarnet, in addition to a ganciclovir implant. Although an off label use, intravitreal administration of ganciclovir and foscarnet are considered standard of care in vision-threatening CMVR. Complications from an intravitreal injection include endophthalmitis, hemorrhage, retinal detachment and cataract. The ganciclovir implant is a sustained release device that is placed in the vitreous cavity, and allows for a high-dose steady state of drug release over 7–8 months. Note that CMVR is associated with an increased mortality risk, and this risk is decreased when the patient is placed on systemic therapy.[4] It is therefore recommended that all patients with active CMVR be placed on systemic therapy, in addition to the possible adjuvant use of local treatment.

Treatment algorithms are based upon location of disease, the patients' experience with HAART, and the resistance or sensitivity of the CMVR to the available medications. In addition, medication can be administered systemically, locally, or in combination. Patients with Zone I disease (CMVR within the vascular arcades) should be treated with intravitreal injections (to be followed by an implant) in combination with systemic antiviral medications. Patients who are HAART-experienced and have persistently low CD4+ cell counts may need reevaluation of their regimen. Any patient with Zone II or III disease (outside the vascular arcades) should be treated with oral valgancyclovir, although patients who are HAART-experienced may benefit from an implant.[5] If the patient does not respond appropriately, ganciclovir resistance testing is warranted.

After resolution of active disease, patients are placed on a follow-up schedule according to their CD-4+ counts. If the lymphocyte count is below 50 cells/μl, patients should be seen on a monthly basis, although the intervals may be increased accordingly as the CD-4+ cell count improves. Termination of therapy may be considered if immune reconstitution takes place, which is defined as a rise of CD-4+ of at least 50 cell/μl to over 100cell/μl. This elevation must be sustained for at least 6 months, with some clinicians waiting one year before discontinuing therapy for CMVR.

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# A 17-Year-Old Female with Peripheral Vision Loss

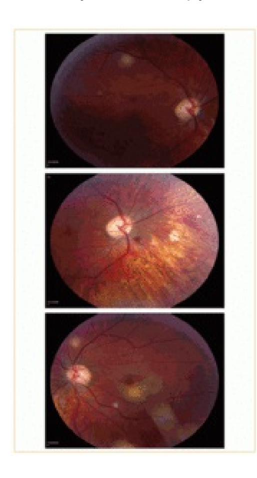
**Chapter:** A 17-Year-Old Female with Peripheral Vision Loss
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0018

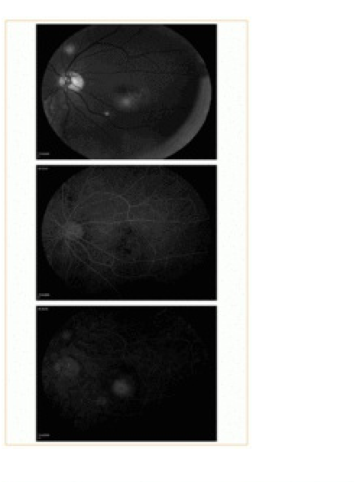
### Presentation and Case History

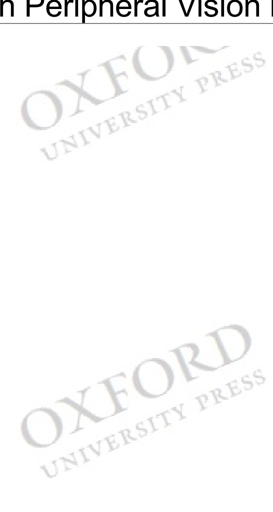
A 16-year-old female from New York City presented with one day of distorted central vision in her left eye. Three weeks prior, she had noticed a non-tender, one-centimeter left neck mass, which resolved after two weeks. She reported no symptoms affecting the right eye, and the left eye was without redness, pain, or discharge. She denied fever, chills, head-ache, or other neurological symptoms. On physical examination, she was afebrile and her other vital signs were unremarkable. Visual acuity in the left eye was 20/50, and dilated fundus examination revealed a retinochoroiditis with active lesions near the fovea (Figures 4d.1 to 4d.6). There was no evidence of anterior segment inflammation.

Several laboratory studies, including erythrocyte sedimentation rate, C-reactive protein, human immunodeficiency virus ELISA, tuberculin skin test, reactive plasma reagin, Lyme antibody, *Toxoplasma* antibodies, and autoimmune studies were unremarkable; however, serologic studies were positive for *Bartonella henselae* (IgM 1:40, IgG positive, no titer available).

On further questioning, the patient reported spending time with her neighbor's kitten and having been scratched multiple times. Her neighbor had experienced fevers, neck and axillary masses, and visual changes three months prior to her presentation. Based on the history, ophthalmologic examination, and serologic evidence, our patient was diagnosed with ocular bartonellosis. She was treated with oral corticosteroids for 2 weeks, but continued doxycycline and rifampin for a total of 6 weeks. Retinal examination of the left eye after therapy showed near resolution of lesions, and visual acuity returned to 20/20 (Figure **4d.7**).











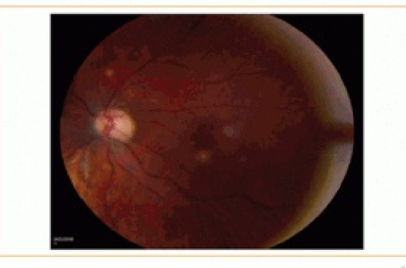





Figure 4d.1 through 4d.7
Dilated funduscopic examination revealed a retino-choroiditis with active lesions near the fovea.

Retinal examination of the left eye after therapy with near complete resolution of the lesions.

**Case 4d Discussion: *Bartonella henselae* Retinitis**

## Clinical Presentation and Diagnosis

The genus *Bartonella* was first described as an erythrocyte-adherent organism in 1909 by Alberto Barton Thompson, a Peruvian microbiologist of English descent. *Bartonella* is a slow-growing, Gramnegative bacillus, and has three main pathogenic species in humans: *B. bacilliformis*, *B. henselae*, and *B. quintana*. *Bartonella bacilliformis* is transmitted by sandfly vectors, and causes Oroya fever and verruga peruana in the Andes mountains. Oroya fever is an acute febrile hemolytic illness, whereas verruga peruana is chronic dermal manifestation that presents months after acute illness. Verruga peruana lesions include miliary, nodular, and mulaire (i.e., blood-filled ulcerative lesions). *Bartonella quintana* is transmitted by the louse tick, and is the cause of trench fever. Additionally, it may cause bacillary angiomatosis (BA), bacillary peliosis (BP), and culture-negative endocarditis in both HIV-infected and uninfected patients. BA is a neovascular proliferative skin and lymphatic disorder, and BP is a disease of hepatic and splenic blood-filled cystic structures. *Bartonella henselae* can cause BA, BP, fever of unknown origin (FUO) in children and the immunocompromised, and cat scratch disease (CSD).[6]

CSD was first described as a syndrome in 1950 as *la maladie des griffes du chat*. There are 22,000 cases of CSD per year in the United States. It generally occurs in immunocompetent individuals, and more commonly in children, adolescents, and young adults.[1] CSD typically manifests as a self-limited regional lymphadenopathy. Patients may initially develop a pustule at the inoculation site, followed by fever and unilateral regional lymphadenopathy within seven weeks of infection; other complaints include anorexia, fatigue, malaise, and headache. Lymphadenopathy usually spontaneously regresses within 2 to 4 months. Disseminated disease occurs in 5%–14% of patients, and presents with atypical manifestations including pneumonitis, splenitis, hepatitis, encephalopathy, cardiac disease, and ocular disease. Prior to the development of effective laboratory techniques, the diagnosis of typical CSD was based on clinical and epidemiologic criteria. With modern PCR and serologic assays, the criteria have evolved to include:

1. History of cat or flea exposure
2. Laboratory (i.e., polymerase chain reaction assay positive) or radiologic (computed topography [CT] scan with liver and/or spleen abscesses) evidence of disease
3. Positive serology tests ⟩1:64 for *B. henselae* or *B. quintana* (i.e., enzyme immunoassay [EIA] or indirect fluorescent antibody assay [IFA])
4. Tissue biopsy with evidence of granulomatous inflammation compatible with CSD or pleomorphic bacilli found on Warthin-Starry silver stain[2]

Serology with EIA or IFA for *B. henselae* with an antibody titer ratio of ⟩1:256 is usually indicative of active infection, whereas a titer ⟩1:64 indicates possible infection. Sensitivity of serologic tests is 90% in immunocompetent patients and 70% in immunodeficient patients. The prevalence of *Bartonella* IgG positivity within the general population is 4%–6%, and lifelong immunity is conferred with one attack of CSD.[2] The differential diagnosis of CSD includes lymphogranuloma venereum, tuberculosis, other mycobacterial infections, bacterial adenitis, tularemia, brucellosis, histoplasmosis, coccidioidomycosis, sarcoidosis, toxoplasmosis, infectious mononucleosis, and benign or malignant tumors (i.e., lymphoma).

Transmission of *Bartonella henselae* from cats to humans has been established by epidemiologic, microbiologic, and PCR studies; the exact role of the flea vector in cat-to-human transmission is still being defined. People are fifteen times more likely to contract CSD when owning more than one kitten younger than 12 months of age, when compared to those who owned older cats. Those scratched by a kitten were 27 times more likely to develop disease. Those having more than one kitten with fleas were 29 times more likely to become infected with *B. henselae* than those owning kittens without fleas.[2]

There are three forms of ocular bartonellosis: (1) Parinaud's oculoglandular syndrome (POS); (2) neuroretinitis: and (3) focal retinochoroiditis.[3] Parinaud's oculoglandular syndrome has been described in up to 5% of patients with CSD, and includes a granulomatous conjunctivitis and ipsilateral preauricular lymphadenitis. POS presents as unilateral eye pain, foreign body sensation, unilateral eye redness, mild eyelid swelling, and possible eye ulceration. Transmission to the eye in ocular bartonellosis is postulated to result from direct inoculation of cat flea feces from hand-to-eye contact. The differential diagnosis of unilateral granulomatous conjunctivitis and POS includes tuberculosis, syphilis, tularemia, sporotrichosis, tularemia, mononucleosis, coccidioidomycosis, and *Chlamydia trachomatis* infection.[3]

Neuroretinitis develops in 1%–2% of patients with CSD, and presents with a sudden loss of visual acuity. It is associated with papilledema and stellate macular exudates,

arranged in a star formation known as the “macular star.” It is a form of optic neuropathy that involves optic disk swelling. Other signs from residual macular lesions include diminished contrast sensitivity and altered color vision. Disease is usually self-limited with mild residual visual deficits. The differential diagnosis for optic disk swelling with a macular exudate star formation includes pseudotumor cerebri, diabetes mellitus, sarcoidosis, syphilis, tuberculosis, toxoplasmosis, toxocariasis, Lyme disease, malignant hypertension, vascular disorders, viral infection, and leptospirosis.

Focal retinochoroiditis can occur with or without macular exudates and optic disk edema. Multifocal lesions usually cause optic disk swelling, and symptoms are similar to those seen in neuroretinitis. Complications involve retinal artery and vein occlusions, along with retinal detachment. Other ocular disease includes optic neuritis and uveitis. The diagnosis of ocular bartonellosis is made by a combination of clinical ophthalmologic findings, blood culture, serologic testing, and PCR of ocular tissue.[3, 4]

## Management

Treatment for typical, localized CSD in immunocompetent patients is generally not indicated, since disease is self-limited. *Bartonella henselae*, in general, is susceptible to beta-lactams, tetracyclines, macrolides, aminoglycosides, fluoroquinolones, vancomycin, rifampin, chloramphenicol, and cotrimoxazole. A five-day treatment with a macrolide antibiotic in immunocompetent patients with CSD has been shown to shorten the duration of symptoms (i.e., measured by lymph node size) in a randomized prospective, placebo-controlled trial.[5] Other 5- to 14-day single antibiotic regimens for CSD include ciprofloxacin, trimethoprim-sulfamethoxazole, and rifampin.

The treatment for ocular bartonellosis is not well defined, and is based on case reports and case series. Given the risk of permanent neurologic deficits, corticosteroids and doxycycline with rifampin are often given for an extended course (i.e., usually 4–6 weeks) based on clinical improvement. In a retrospective case series of seven patients with *Bartonella* neuroretinitis treated with both doxycycline 100 mg and rifampin 300 mg oral tablets every 12 hours, all but one patient regained baseline vision within 4 weeks. All patients were treated with less than 2 weeks of oral corticosteroids, and were treated with antibiotics for 4–6 weeks. Rifampin is advantageous in this setting because of its adequate penetration of the blood–brain barrier. The authors concluded that a prompt initiation of antibiotic treatment may shorten the course of ocular disease.[4] Recommendations extrapolated from case reports suggest a longer duration of treatment with antibiotics (i.e., up to 4 months) in the immunocompromised patient, and a shorter duration (2 weeks) in immunocompetent patients.[3]

In order to prevent disease, declawing and routine nail clipping of kittens is recommended. In addition, cat flea control, regular care of the litter box, proper hand hygiene after close contact with kittens and cats, and cleaning scratches and bites with soap and water may decrease the likelihood of *Bartonella* transmission.[2]

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## Fever, Chills, and Unilateral Vision Loss in a 73-Year-Old Man

**Chapter:** Fever, Chills, and Unilateral Vision Loss in a 73-Year-Old Man
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0019

### Case Presentation

A 73-year-old man with a history of benign prostatic hypertrophy presented with sudden loss of vision of the right eye on the day of admission. He also noted pain and tearing of the eye, but denied exacerbation of the pain when moving the eye. He had not had any trauma to the eye and did not wear contact lenses. For 12 days prior to presentation he felt fatigue, mild dyspnea, and fevers up to 38.5? Celsius. He also had been having night sweats and weight loss that he estimated to be 10 pounds over the preceding few weeks.

On physical examination, his temperature was 37.3°C and his blood pressure was as low as 88/63 before hydration. The right eye had conjunctival erythema and tearing with a visible hypopyon (Figure **4e.1**). His visual acuity on the right eye was limited to hand movements, while on the left eye it was 20/60. The retinal exam on the left was normal, but the degree of vitreous clouding in the right eye did not allow for visualization of the retina. No conjunctival petechiae or other stigmata of infectious endocarditis were noted, but the patient was found to have a III/VI holosystolic murmur heard loudest at the apex. The patient's laboratory values were significant for a mild anemia (hemoglobin, 13 gm/dl) and leukocytosis (11.3 × $10^3$ WBC/μl).



Figure 4e.1
Right eye examination revealing injected conjunctiva and hypopyon.

Multiple blood cultures and cultures of the anterior chamber fluid were positive for gram positive cocci in pairs (Figure **4e.2**). The organism was identified as *Streptococcus bovis* with negative PYR testing, absence of growth in 6.5% saline, and hydrolysis of starch. A transesophageal echocardiogram revealed a ruptured P2 scallop of the posterior mitral valve leaflet, with long mobile components consistent with vegetation or destroyed mitral valve resulting in moderate mitral regurgitation (Figure **4e.3**). The patient underwent mitral valve replacement, vitrectomy, and installation of intravitreous vancomycin. He was discharged with 4 weeks of intravenous penicillin and subsequently returned to his home in Venezuela, where he was to have a colonoscopy for further evaluation for gastrointestinal pathology.

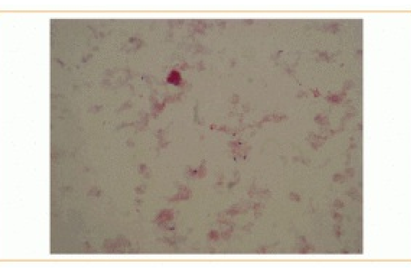




Figure 4e.2
Gram stain of blood culture revealing small Gram-positive cocci in pairs (original magnification 100x).

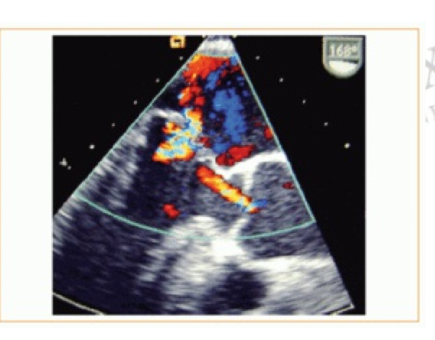




Figure 4e.3
Transesophageal echocardiogram revealing ruptured P2 scallop of the posterior mitral valve leaflet with long mobile components consistent with vegetation or destroyed mitral valve resulting in moderate mitral regurgitation.

**Case 4e Discussion: *Streptococcus bovis* Endophthalmitis**

## Clinical Features and Diagnosis

Endophthalmitis represents infection of the vitreous or aqueous humor, or both. It may be classified by the route of infection: either endogenous endophthalmitis or exogenous endophthalmitis. Exogenous endophthalmitis may be caused by surgical procedures, trauma to the eye, or by keratitis that progresses posteriorly. Endogenous endophthalmitis is the result of hematogenous spread of organisms from endovascular sites, such as infected heart valves. Bacteria (including viridans group streptococci, beta-hemolytic streptococci, and staphylococcal species) represent the majority of cases of endogenous endophthalmitis, but fungi may also cause this vision-threatening infection (see Case 4f).[1] A mucoid strain of *Klebsiella pneumoniae* that has been noted to cause a syndrome of liver abscess, pulmonary abscess, and endophthalmitis, has been described in Taiwan.[1]

Clinical signs of endophthalmitis may include eye pain, redness, and sudden visual loss. Most patients with exogenous endophthalmitis do not have fever or other systemic signs and symptoms of infection, but those with endogenous endophthalmitis are likely to have positive blood cultures and systemic signs of inflammation.[1] The diagnosis may be supported by positive blood cultures in the case of endogenous endophthalmitis, but vitreous cultures are often needed for confirmation. Gram stain of the vitreous fluid may indicate the most likely pathogen, even before cultures are positive.[1]

*Streptococcus bovis* was first associated with gastrointestinal malignancies in the late 1970s, and the association was subsequently confirmed in several studies. In a study of 278 patients, *S. bovis* fecal carriers were more likely to have carcinoma of the colon than controls with other nonenterococcal bacteria.[2] A subsequent study of 29 patients also confirmed the link between *S. bovis* septicemia and carcinoma of the colon, and emphasized the need for colonoscopy in patients from whom the organism is isolated.[3] Recent taxonomic reclassification of the *Streptococcus bovis* group has led to some confusion. The new name *Streptococcus gallolyticus* has replaced *S. bovis,* and three subspecies (*gallolyticus, pasteurianus*, *macedonicus*) replaced the biotypes of *S. bovis*.[4] For the purposes of this discussion, the two species names will be used interchangeably. The organisms are part of the nonenterococcal group of Group D streptococci that are characterized microbiologically by their growth in the presence of 40% bile, hydrolysis of esculin, and inability to grow in 6.5% sodium chloride.[2] S. *bovis* is responsible for approximately 17% of infectious endocarditis cases, and it is not associated with increased morbidity or mortality when compared to other streptococcal causes of endocarditis, beyond the association with colonic malignancy.[5]

Two case reports describing *Streptococcus bovis* endogenous bacterial endophthalmitis highlight the rarity of this organism as a cause of eye infections. In one of the cases, the eye findings were the initial presentation of colon cancer. In the second case, the patient was an elderly man known to have liver cancer.[6, 7] In both cases, the diagnosis was confirmed by positive cultures of the blood and the vitreous fluid. In one case, the patient was managed with a combination of vitrectomy, intravitreous antibiotics, and intravenous antibiotics, while in the second, the patient had signs of severe sepsis and required enucleation.[6, 7]

## Management

Exogenous endophthalmitis is usually managed with intravitreous antibiotics, along with vitrectomy in severe cases. Endogenous endophthalmitis requires a combination of systemic and intravitreal antibiotics. Vitrectomy is generally reserved for fulminant cases, as well as those that fail to respond to 24 hours of intravitreous vancomycin and amikacin.[1] Most *Streptococcus bovis* isolates are susceptible to penicillin (MIC (0.1 mg/l) but, due to variations in minimal inhibitory concentrations, susceptibility testing should guide therapy.

Endocarditis can be managed, in some cases with several weeks of systemic antibiotics alone, but, in some cases surgical intervention may be required. Indications for surgery include patients with ring abscess, refractory bacteremia, multiple embolic events, and heart failure. In this case, the valve was replaced because of valve perforation and concern for further embolic events. Given the strong association between gastrointestinal pathology and *Streptococcus bovis* bacteremia, patients who are found to have positive cultures with this organism should be evaluated with colonoscopy.

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

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# Decreased Vision and a Painful, Red Eye in a Patient with Acute Myelogenous Leukemia (AML) and Prolonged Neutropenia

**Chapter:** Decreased Vision and a Painful, Red Eye in a Patient with Acute Myelogenous Leukemia (AML) and Prolonged Neutropenia
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0020

## Presentation and Case History

A 46-year-old male with refractory AML was admitted for chemotherapy. He had previously received an allogeneic stem cell transplant from an HLA-identical sister, but subsequently relapsed. His treatment course was previously complicated by severe graftversus-host disease involving skin, liver, and gastrointestinal tract that required high-dose corticosteroid therapy. The patient's medications included tacrolimus and prednisone, as well as prophylactic valacyclovir, levofloxacin, and voriconazole.

On physical examination, the patient was afebrile with oral thrush and mild, diffuse wheezing. The remainder of his examination was unremarkable. His admission laboratory values were significant for pancytopenia (hemoglobin 11.3 g/dl; white blood cell count 3.9 × $10^3$/μl, absolute neutrophil count 400 cells/μl; platelets 54 × $10^3$/μl) and elevated liver enzymes (aspartate aminotransferase 58 units/l; alanine aminotransferase 120 units/l). Voriconazole was discontinued due to the liver function abnormalities, and caspofungin was initiated for antifungal prophylaxis.

After starting reinduction chemotherapy, the patient developed prolonged neutropenic fever. He was treated with broad-spectrum antibiotics, and liposomal amphotericin B was substituted for caspofungin due to a worsening nodular infiltrate on chest CT (Figure **4f.1**). The antibiotics and amphotericin B were continued and, in approximately one month, fevers resolved. He subsequently developed tender, subcutaneous nodules on his lower extremities, and a skin biopsy was performed (Figures **4f.2**, **4f.3**, and **4f.4**). Based on the presence of fungal hyphae consistent with *Aspergillus,* his antifungal therapy was changed to voriconazole; however, two days later he developed pain, redness, and decreased vision in his right eye (Figure **4f.5**).





Figure 4f.1
Chest CT, axial view revealing worsening right lower lobe nodular consolidation.





Figure 4f.2
Leg with tender, subcutaneous nodules and non-blanching macules.



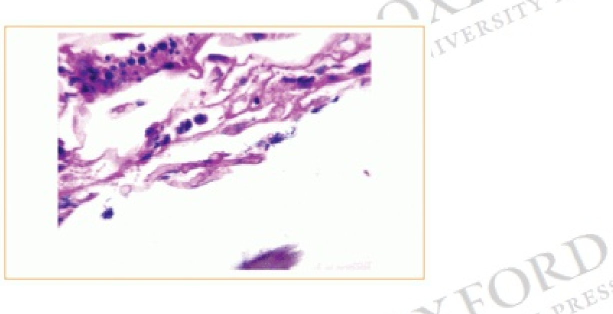





Figure 4f.3
Skin biopsy. Periodic acid-Schiff stain revealing septated hyphae (original magnification 100x).

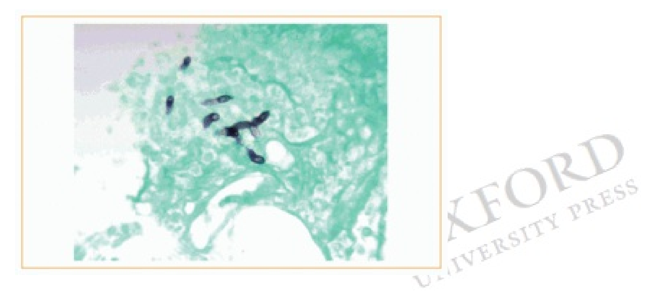


Figure 4f.4
Skin biopsy. Gomori methenamine silver stain revealing branching, septated hyphae (original magnification 100x).

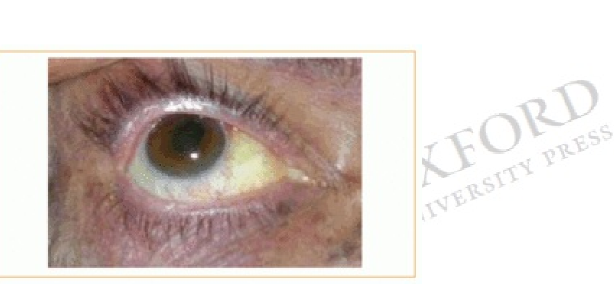


Figure 4f.5
Eye examination revealing injected conjunctiva of right eye.

Ophthalmologic exam revealed marked vitreal infiltrates, and aspiration of vitreous fluid was performed for culture. Intravitreal amphotericin B was administered for presumed fungal endophthalmitis. His vision continued to worsen to light perception only. At this time, intravitreal voriconazole was administered based on the vitreal cultures, and a vitrectomy was performed. Unfortunately, the patient failed extubation after the procedure and subsequently expired. The cultures from both the skin and the vitreal cavity grew *Aspergillus fumigatus* (Figures **4f.6** and **4f.7**).



Figure 4f.6
Vitreous culture, macroscopic colony appearance on Sabaroud’s dextrose agar.

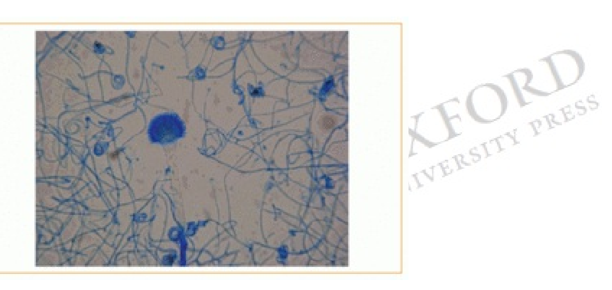




Figure 4f.7
Vitreous culture, microscopic appearance of fruiting head stained with lactophenol blue (original magnification 40x).

**Case 4f Discussion: *Aspergillus fumigatus* Endophthalmitis**

## Clinical Features and Diagnosis

Endogenous Fungal Endophthalmitis (EFE) is predominantly due to *Candida albicans* (56%) and *Aspergillus* species (24%).[1] *A. fumigatus* and *A. flavus* comprise the majority of *Aspergillus* infections. The major risk factors for *Aspergillus* EFE are primary pulmonary infection or disseminated disease in an immunocompromised host, corticosteroid use, broad-spectrum antibiotics, and intravenous drug use. *Aspergillus* EFE has faster progression from symptoms to visual loss (5 days) compared to *Candida* EFE (61 days) and has a much worse visual prognosis.[1] One case series by Essman et al. reported that 76% of patients with *Candida* endophthalmitis responded to standard treatment, consisting of systemic and intravitreal amphotericin B and vitrectomy, with a visual acuity of 20/400 or better compared to 0% of patients with *Aspergillus* EFE.[2]

Patients with EFE present most commonly with decreased or blurry vision, redness, and pain in the affected eye. Ophthalmologic exam of the anterior chamber often reveals significant injection and a corresponding hypopyon. Evidence of vitritis in the posterior chamber is also common, particularly in *Aspergillus* EFE. In addition, a pseudo-hypopyon (gravitational layering of subretinal inflammatory cells) is considered by some as pathognomonic for *Aspergillus* EFE, although it is found in only 11% of patients with this infection.[3] Retinal findings including cotton wool spots, Roth spots, and hemorrhages, and choroidal and vitreal infiltrates are found in 40% of patients with EFE.[3] In *Aspergillus* EFE, the central macula is often involved and accounts for the poor visual prognosis.

Diagnosis requires clinical suspicion and immediate ophthalmologic examination to obtain cultures. Cultures from the anterior chamber are diagnostic only one-third of the time. Therefore, it is frequently necessary to culture the vitreous fluid or vitrectomy fluid, which are diagnostic in up to 90% of patients with EFE.[3] Although *Aspergillus* EFE often develops from disseminated disease, blood cultures are diagnostic in only 20% of cases.[1] As in this case, cultures from other sites, such as skin or from bronchoscopy, can also be helpful. The use of polymerase chain reaction (PCR) has been shown to be more sensitive than traditional methods in detecting fungal infections. However, since many labs do not support PCR analysis, and PCR does not provide susceptibility data, traditional methods must still be applied.[1]

## Treatment

Treatment of EFE has consisted of a combination of systemic antifungal medications, intravitreal amphotericin B, and vitrectomy. Intravenous amphotericin B, traditionally used in disseminated fungal infections, has poor penetration into the vitreous cavity, and although intraocular levels may be higher when using the liposomal formulation, the data is inconclusive in humans.[4] The treatment of EFE, therefore, also requires intravitreal administration of amphotericin B in doses of 5–10 μg.[1] Since intravitreal amphotericin B has been reported to have retinal toxicity in animal studies, there has been interest in discovering alternative antifungal agents that maintain a broad spectrum of coverage. Systemic fluconazole and flucytosine have adequate intraocular penetration but are limited by resistance, especially with *Aspergillus* species.[1] Voriconazole given orally or intravenously has been found to have intravitreal concentrations well above minimal inhibitory concentrations for most *Candida* and *Aspergillus* species. In addition, it appears to be safe for intraocular use, without evidence of retinal toxicity even at high concentrations in the eye. There are now multiple case reports citing the efficacy of systemic and intravitreal voriconazole in treating *Aspergillus* EFE that has failed prior conventional antifungal therapy.[5]

Surgical treatment with vitrectomy is often necessary, especially in cases with marked vitreal involvement, which is typical in *Aspergillus* EFE.[6] Prompt vitrectomy in these cases is not only diagnostic but also necessary to debulk the vitreal cavity and remove the infecting organism. Vitrectomy has been associated with improved visual acuity and resolution of infection in cases of *Aspergillus* EFE, and is recommended along with systemic antifungal therapy with liposomal amphotericin B or voriconazole in cases of disseminated infection.[1,3] If an *Aspergillus* species is confirmed as the pathogen via vitrectomy culture, a second injection of intravitreal amphotericin B should be given, as the half-life of amphotericin B postvitrectomy is shortened from 7–10 days to only 2 days.[3] Repeat vitrectomy and injections may be needed depending on the resolution of infiltrates in the posterior chamber. Systemic antifungal therapy should be continued for at least 4 weeks and until the disseminated infection has resolved.[3]

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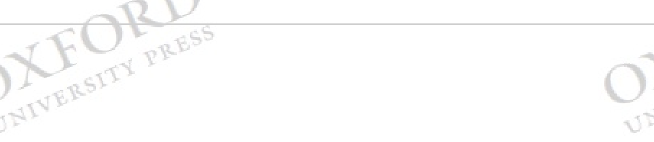



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## Blurry Vision in a Patient with AIDS

**Chapter:** Blurry Vision in a Patient with AIDS
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### Clinical Presentation

A 56-year-old woman with HIV/AIDS was referred to ophthalmology for distorted vision in the left eye. She had been diagnosed with HIV/AIDS eight months prior to her presentation, and her CD4+ cell count had increased while taking atazanavir, ritonavir, and tenofovir-emtricitabine from 4 cells/μl at the time of diagnosis to 102 cells/μl at the time of presentation. She had a history of HIV-associated neuropathy and *Candida* esophagitis, but had never been treated for an ocular opportunistic infection.

On examination, her vision was 20/50 with some metamorphopsia. The examination of the right eye was unremarkable, but the left eye was noted to have 1+ anterior chamber inflammation, in addition to 1+ vitreous cells. She was found to have a large chorioretinal scar, originating at the optic nerve and following the course of the superior temporal arcade. The involved area extended within one-half disc diameter of the fovea, but did not involve the fovea. The lesion was consistent with inactive CMV retinitis (CMVR) (Figure **4g.1**). There was no evidence of active disease at this time; vitreous cells were noted to overlie the lesion.



Figure 4g.1
Fundoscopic examination of left eye revealed sharp optic nerve margins, sheathed vessel along superior arcade, chorioretinitis scar, and retinal pigment epithelium mottling in posterior pole.

Ocular coherence tomography (OCT) was performed, and showed cystoid macular edema (Figure **4g.2**), which was also demonstrated on fluorescein angiography (Figure **4g.3**). Her CD4+ cell count had been steadily trending upward since diagnosis. In the context of an inactive lesion of CMVR, associated with both anterior and vitreous inflammatory cells, structural retinal changes, and an increasing CD-4$^+$ count now over 100 cells/μl, the diagnosis of immune reconstitution syndrome was made.

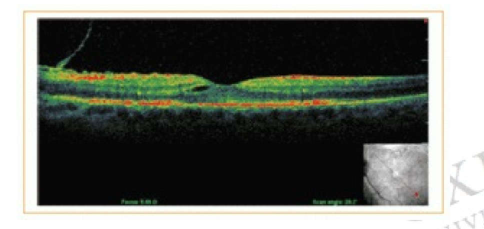




Figure 4g.2
Ocular coherence tomography (OCT) showing cystoid macular edema.

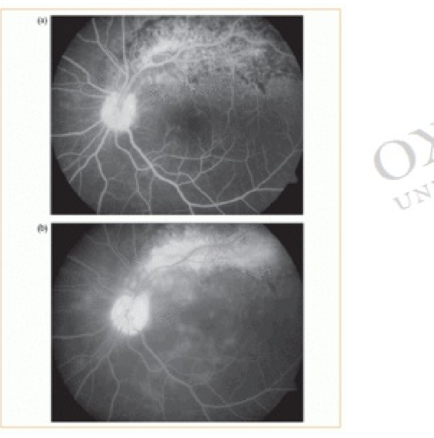








Figure 4g.3a and 3b
Fluorescien angiography showing large CR scar along superiortemporal arcade, with late staining along areas of scarring, no leakage, window defects in macula that stain late and correspond to retinal pigment epithelium mottling, associated cystoids macular edema, and no leakage from disc.

The patient was treated with topical prednisolone acetate; however, on repeat examination one month later, the patient was noted to have a decrease of vision to 20/80, with a subsequent increase of both intraretinal edema and cystoid changes on clinical and OCT examination (Figure **4g.4**). Her CD-4$^{+}$ count had risen to 136cells/ml. These changes persisted for 4 weeks and, at that time, an intravitreal injection of triamcinolone acetate, 40mg/0.1ml was performed. Vision improved to 20/40, anterior and vitreous inflammation resolved, and cystoid changes and retinal edema decreased significantly, both clinically and on OCT (Figure **4g.5**).

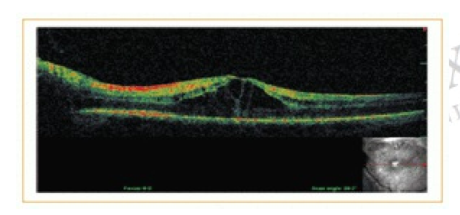


Figure 4g.4
Ocular coherence tomography (OCT) showing increase in cystoid macular edema.

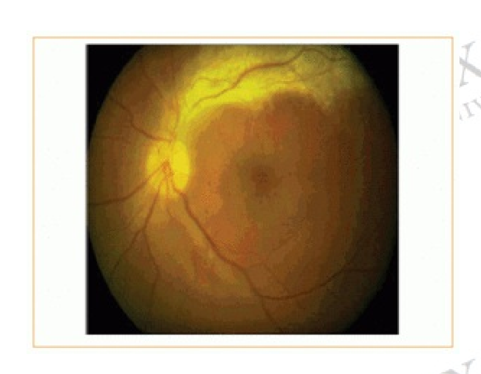




Figure 4g.5
Fundoscopic examination showing increase in cystoid macular edema (CME).

The patient's vision remained stable over the course of a year, with topical steroids being tailored to the clinical status until she was ultimately tapered off all ocular medications.

**Case 4g Discussion: Immune Reconstitution Uveitis**

## Clinical Features and Diagnosis

Immune reconstitution uveitis (IRU) is a syndrome characterized by increased ocular inflammation, both anterior and in the vitreous, in patients with a now-quiescent intraocular infection, who have experienced immune recovery.[1] It is sometimes considered a subset of immune reconstitution syndrome, seen in a number of HAART-treated patients, who exhibit a paradoxical deterioration in their clinical status as their immune status improves. Although most commonly seen in patients with inactive CMV retinitis, it has been noted in patients with ocular toxoplasmosis, tuberculosis, cryptococcosis and leishmaniasis. IRU is thought to occur as a response to intraocular antigens; therefore, patients with unilateral inactive CMVR are only at risk in that eye. IRU occurs in the early stages of immune recovery[2] and has been noted to occur between 2 and 26 weeks after initiation of antiretroviral therapy, with the median at 4 weeks.[3]

IRU is not uncommon; it was found in 9.6% of 259 patients with inactive CMV retinitis and immune recovery, in an Longitudinal Study of Ocular Complications of AIDS (LSOCA) study.[4] It is seen in the context of immune recovery, undetectable CMV DNA or HIV RNA levels in blood, history of intraocular infection with no currently active disease, and often in patients taking antiretroviral medications to treat previously active lesions. Large lesions are thought to predispose the patient to IRU, as the larger the area of infected retina is, the larger the subsequent antigen load will be, thereby increasing the odds of an inflammatory reaction.[1] These patients are also less likely to be on anti-CMVR treatment.[1] IRU is associated with moderate to severe vision loss, with these patients having over a 20-fold higher risk of cystoid macular edema, in addition to an increased risk of epiretinal membrane (ERM) formation and cataract.[1]

Early signs and symptoms of IRU include anterior and/or vitreous inflammatory cells, floaters, posterior synechiae and optic disc edema, all of which can cause decreased vision. This must be recognized promptly and treated aggressively to prevent late complications. The mainstay of therapy is steroids, given either topically, intravitreally or systemically, which have an approximate 50% success rate. If there is only mild to moderate anterior and vitreous inflammation with no structural changes, topical steroids (prednisolone acetate 1%) are recommended; however, the patient must be monitored closely, as any early structural or anatomic change (CME, ERM, etc.), must be addressed immediately. This warrants treatment with either systemic steroids (1mg/kg initially) or intravitreal injection (triamcinolone acetate 40mg/0.1ml). These therapies all have potentially significant complications, and the patient must be monitored appropriately. There is some evidence to suggest that the institution of anti-CMVR therapy may be of use, as it decreases antigen load and thus may facilitate control of inflammation.[5]

Late manifestations leading to moderate vision loss include cystoid macular edema (CME; Figures **4g.2** and **4g.3**), ERM (Figure **4g.6**), vitreoretinal traction (VRT) (Figure **4g.7**), and neovascular membrane formation (NVE), in addition to cataract. CME, ERM, and NVE can all be treated with steroids, either intravitreal or systemic. Surgical intervention may be necessary to treat ERM, VRT, and cataract.

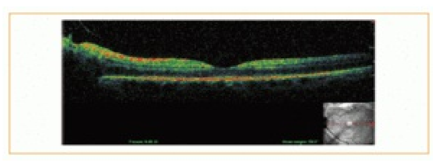
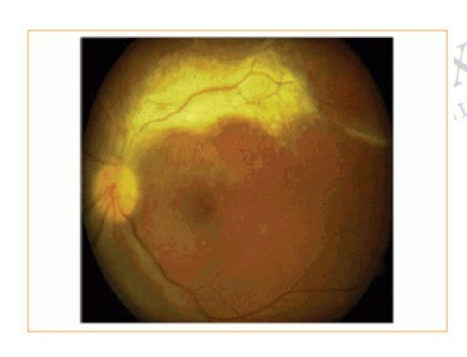




Figure 4g.6
Ocular coherence tomography (OCT) showing resolution of cystoids changes.



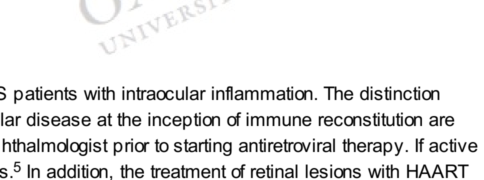


Figure 4g.7
Fundoscopic examination showing resolution of cystoid changes.

IRU is an entity that may be difficult to diagnose and treat, but is of utmost importance in the evaluation of HIV/AIDS patients with intraocular inflammation. The distinction between active disease and IRU is further complicated by evidence demonstrating that patients with untreated ocular disease at the inception of immune reconstitution are predisposed to the development of IRU. It is, therefore, recommended that all patients with AIDS be seen by an ophthalmologist prior to starting antiretroviral therapy. If active disease (CMVR, for example) is found, it is recommended that it be treated before the patient initiates antiretrovirals.[5] In addition, the treatment of retinal lesions with HAART may indeed result in inactive disease at some point, but at the risk of a larger retinal lesion, which in turn puts the patient at higher risk for the development of IRU.[5] Patients may need multiple courses of therapy for IRU, and careful monitoring over time with attention to even minimal changes in intraocular inflammation, as these can lead to structural and anatomic changes in the eye and, ultimately, decreased vision.

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## A 43-Year-Old Man with Neck Swelling and Stridor

**Chapter:** A 43-Year-Old Man with Neck Swelling and Stridor
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 43-year-old man presented to an outside hospital with a 2-day history of tooth pain, and subsequent left-sided neck swelling and difficulty swallowing (Figure **5a.1**). He had a past medical history of alcoholic cirrhosis and chronic renal insufficiency, but was taking no medications. He had recently moved to the United States from Turkey, one year prior to presentation. In the emergency department, a computed tomography scan of the neck showed necrotizing cellulitis consistent with Ludwig's angina (Figure **5a.2**). Surgery was recommended, but the patient left against medical advice. He returned several hours later for a second opinion, and at this time he was noted to have stridor and voice changes.



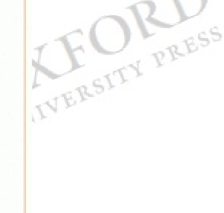


Figure 5a.1
Physical examination revealed marked neck swelling.





Figure 5a.2



CT scan neck, axial view showing emphysematous changes in the soft tissues consistent with a necrotizing infection.



On physical examination, he was afebrile with temperature of 36°C., with normal heart rate and blood pressure; room air saturation was 100% on pulse oximetry. He was noted to have scleral icterus, poor dentition, and trismus with elevation of the tongue and "woody" edema of the floor of the mouth. He had bilateral brawny edema of the neck, but no crepitus was palpated. The patient was intubated under fiberoptic guidance and taken to the operating room by ENT for incision and drainage of a submandibular abscess. In addition, oral maxillofacial surgery extracted four teeth with gross caries.

The patient was treated with ampicillin-sulbactam, but remained persistently febrile, and the antibiotics were changed to vancomycin, imipenem, and clindamycin. Microscopic examination of the purulent drainage from the abscess revealed a mixed flora consisting of many Gram-positive cocci in pairs and chains, and many Gram-negative rods (Figure **5a.3**). Aerobic and anaerobic cultures from the operating room grew *Streptococcus constellatus*, group F beta-hemolytic *Streptococcus*, and *Prevotella buccae*. He eventually defervesced after a repeated bedside washout of wound, and was eventually transitioned to oral amoxicillin-clavulanate for completion of several weeks of antibiotic treatment.

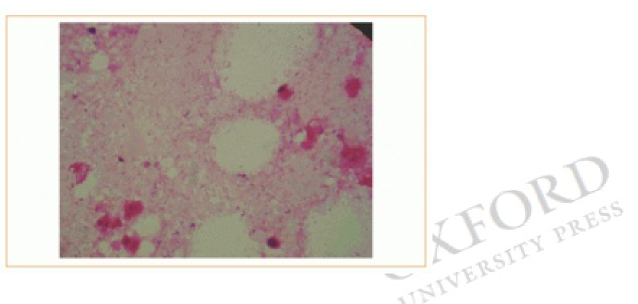


Figure 5a.3
Gram stain of purulent drainage from the abscess revealed a mixed flora consisting of many Gram-positive cocci in pairs and chains and many Gram-negative rods (original magnification 1000x).

**Case 5a Discussion: Ludwig's Angina**

## Head and Neck Infections

While infections of the head and neck are relatively uncommon in the post-antibiotic era, infections of three particular spaces in the head and neck are of primary importance, as they can be life-threatening in certain circumstances. These "space infections" are categorized by three locations—submandibular, lateral pharyngeal, and the retropharyngeal/danger/prevertebral spaces. Understanding the anatomy of these particular spaces provides insight into the clinical manifestations and management of these infections. The submandibular space is bordered anteriorly and laterally by the mandible, and inferiorly by the deep cervical fascia. The mylohyoid muscle separates the submandibular space into the sublingual and submylohyoid space. Infections in this space are typically odontogenic in nature, and include Ludwig's angina as described in the patient above.[1]

The other two spaces include the lateral pharyngeal space, which is a 2.5 cm long inverted cone extending from the hyoid to the sphenoid bone. It is bordered laterally by the parotid gland, mandible, and the attached internal pterygoid muscle. Its medial wall is contiguous with the carotid sheath, which contains the vital structures of the internal carotid artery, the internal jugular vein, and the vagus nerve. Infection of the lateral pharyngeal space may result from pharyngitis, tonsillitis, parotitis, otitis, or mastoiditis, as well as from ondontogenic infection.[1]

Lastly, the retropharyngeal/prevertebral/danger space is located between the posterior aspect of the pharynx/esophagus and the anterior portion of the spine. The retropharyngeal space is most anterior and extends from the base of the skull to the C7/T1 region. Infections in the retropharyngeal space can spread to the superior anterior mediastinum, resulting in pleural and pericardial infections. The danger space is located posterior to the alar fascia, and is bounded posteriorly by the prevertebral fascia. The prevertebral space is bound posteriorly by the vertebral bodies, and anteriorly by the prevertebral fascia. It extends from the base of the skull down to the coccyx, and infections in this space usually develop after cervical spine infections from hematogenous seeding, or from contiguous spread from vertebral osteomyelitis. Unlike other infections in the head and neck, which are primarily mixed infections of oropharyngeal origin, in prevertebral infections *Staphylococcus aureus* can play a prominent role.[1]

## Ludwig's Angina

Ludwig's angina refers to the rapidly spreading cellulitis and potentially lethal infection involving the submandibular and sublingual space. It was first described in 1836 by Wilhelm Friedrich von Ludwig, who observed five patients develop "gangrenous induration of the connective tissues of the neck which advances to involve the tissues which cover the small muscles between the larynx and the floor of the mouth." He described a rapidly spreading cellulitis with subsequent airway obstruction, resulting in a 60% mortality rate. The term "Ludwig's angina" was coined one year later, and is derived from the Latin term *angina* to describe the terrible suffocation observed in these patients.[2]

In the pre-antibiotic era, mortality was extremely high and therapy consisted of emergent surgery in order to avoid airway obstruction; despite this, mortality rates of 40%–80% were described. Since then, the combination of systemic antibiotic therapy and aggressive surgical intervention with airway protection has reduced the mortality to 0%–4%. Odontogenic infection is the source of infection in Ludwig's angina in the majority of cases, and usually derives from the second or third molar teeth. Although most infections occur in healthy individuals, certain predisposing factors have been described, including diabetes mellitus, neutropenia, aplastic anemia, glomerulonephritis, and certain immunodeficiencies. Ludwig's angina can also follow after post-traumatic infection from fracture of the mandible, penetrating injury to the floor of the mouth, or even trauma from intubation.[3]

Patients classically present with tooth pain and describe poor dental hygiene or recent dental work. Symptoms include progressive upper bilateral neck pain and swelling resulting in trismus, dysphagia and dysphonia with the classic "hot potato" voice. Patients often have systemic signs and symptoms, including fever and tachycardia, and appear toxic. On exam, there is brawny swelling of the submandibular space that is not pitting. In addition, there is classically "woody edema" of the base of the mouth that results in protrusion of the tongue. Examination of the neck may reveal crepitus, but fluctuation and lymphadenopathy are usually absent. Frequently, tachypnea, stridor and cyanosis usually signal impending airway obstruction and need for emergent airway access.[4]

Diagnosis is usually made clinically, but imaging may be helpful in providing localization of an abscess or finding an odontogenic focus. Plain radiographs may demonstrate the extent of the swelling, as well as reveal gas indicating an anaerobic infection. CT or MRI will confirm airway edema and help localize any fluid collection.

Management in Ludwig's angina most importantly involves securing a stable airway. Blind endotracheal intubation is usually not advised because of complications secondary to trismus, pooled secretions, and altered airway anatomy. Intubation under fiberoptic guidance, while the patient is awake, allows for intubation under visualization. Otherwise, tracheostomy can also be performed with the use of local anesthetic; use of paralytics is generally avoided because it may precipitate occlusion of the airway secondary to loss of tone of the pharyngeal musculature.[4]

Antibiotic therapy is an important component of management, and should cover mixed aerobic and anaerobic organisms associated with oral flora. Initial regimens should cover beta-lactamase-producing aerobic organisms, as well as anaerobic Gram-positive cocci and Gram-negative bacilli; therefore, a penicillin-derivative/beta lactamase inhibitor combination such as ampicillin/sulbactam or piperacillin/tazobactam, would be appropriate. There have been reports of *Klebsiella pneumoniae* in patients with diabetes mellitus from the Asian literature; therefore, carbapenems may also be an appropriate initial choice. Other initial recommended antibiotic regimens include clindamycin with Gram-negative coverage or third- or fourth-generation cephalosporins with metronidazole. In addition, if methicillin-resistant *Staphylococcus aureus* is a concern in a colonized individual, it may be reasonable to add vancomycin as well. *Candida* and *Aspergillus* species have also been reported in a small number of patients.[3]

Lastly, surgical incision and drainage of any purulent collections is a necessary part of the management of these infections. Drains are often left in place to allow for continued drainage of purulent material. In addition, extraction of any teeth with gross caries should be carried out, as this serves as a likely nidus for these infections. With a combination of surgical intervention, antibiotic therapy and airway management, many patients with Ludwig's angina can make a successful recovery.

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## Sore Throat and Neck Swelling in a 48-Year-Old Man with AIDS

**Chapter:** Sore Throat and Neck Swelling in a 48-Year-Old Man with AIDS
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 48-year-old man with AIDS developed worsening sore throat, fever, chills, and neck swelling over the course of three weeks. His lowest CD4+ cell count had been 194 × $10^3$ cells/μl, but his most recent count several weeks earlier had been 452 × $10^3$ cells/μl. His symptoms had improved slightly when he took several doses of his wife's penicillin, but then dramatically worsened when he ran out of the antibiotic. He was originally from Puerto Rico, but he had not traveled recently and had no known history of tuberculosis.

On evaluation in the emergency department, he was noted to have a large left-sided neck mass and an overlying cellulitis (Figures **5b.1 and 5b.2**). He was febrile (temperature, 39.5°C) and tachycardic (heart rate 136), but no stridor was noted. His laboratory examinations were notable for a leukocytosis of 31 × $10^3$ WBC/μl (89% polymorphonuclear cells). Computed tomography of the neck revealed multiple enhancing lymph node abscesses with surrounding edema. The abscesses were as large as 3.4 cm and were displacing the carotid artery and internal jugular vein on the left (Figure **5b.3**). Ampicillin/sulbactam and intravenous vancomycin were initiated, and the patient underwent surgical drainage of the abscesses.

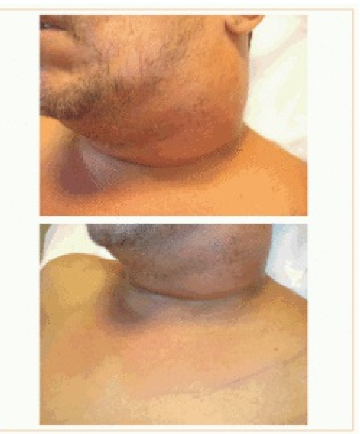








Figure 5b.1 and 5b.2
Physical examination revealed a large left-sided neck mass with overlying cellulitis.



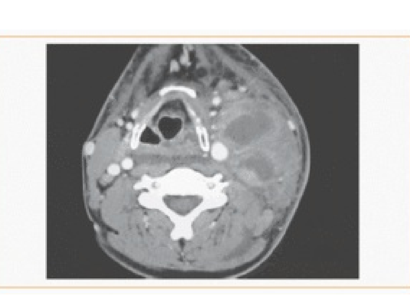



Figure 5b.3
CT scan of the neck, axial view revealed multiple enhancing lymph node abscesses with surrounding edema. The abscesses were as large as 3.4 cm and were displacing the carotid artery and internal jugular vein on the left.

Operative drainage of the abscesses revealed several milliliters of pus from each abscess. Gram-positive cocci in short chains were noted on Gram stain of the material (Figure **5b.4**), and *Streptococcus pyogenes* (beta-hemolytic Group A streptococcus) was recovered in cultures (Figures **5b.5** and **5b.6**). The patient required a second debridement procedure to further drain the abscesses, but eventually recovered after the two surgeries and intravenous ampicillin/sulbactam, followed by oral amoxicillin/clavulanate for 4 weeks.

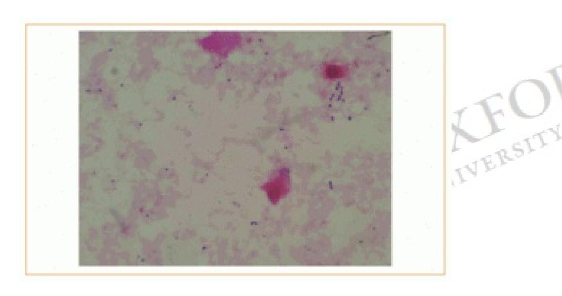


Figure 5b.4
Gram stain of fluid from abscess revealed Gram-positive cocci in short chains.





Figure 5b.5
Sheep's blood agar plate with beta-hemolytic colonies.







Figure 5b.6
Gram stain of cultured material with Gram-positive cocci in long chains.

**Case 5b Discussion: *Streptococcus pyogenes***

## Clinical Features and Diagnosis

*Streptococcus pyogenes* (Group A beta-hemolytic streptococcus) is an organism capable of producing human disease both directly as an invasive pathogen and indirectly via the immune-mediated responses to its antigens. As a directly invading pathogen, it is the most common bacterial cause of pharyngitis, and rarely can become life-threatening when airway is compromised. It is also the causative agent of soft tissue infections that range from simple cellulitis, erysipelas, and impetigo, to necrotizing fasciitis. In the case of necrotizing fasciitis, the organism rapidly spreads through subcutaneous tissues, and it secretes superantigens that nonspecifically activate T-cells resulting in massive tissue inflammation and necrosis.[1]

Toxic shock syndrome is closely related to necrotizing fasciitis, in that a nonspecific activation of the immune system results from the release of streptococcal exotoxins that act as superantigens. This syndrome is characterized by hypotension, tachycardia, fever, a diffuse rash with subsequent desquamation, and end organ damage. The evidence of end organ inflammation may be seen with acute kidney injury, elevated liver enzymes, vomiting and diarrhea, altered mental status, or thrombocytopenia.[1]

The nonsuppurative complications of *Streptococcus pyogenes* infection include post-streptococcal glomerulonephritis and rheumatic fever. Glomerulonephritis is an active inflammation of the kidneys that results from the deposition of immune complexes in the basement membrane following an episode of streptococcal pharyngitis or skin infection. Rheumatic fever occurs only after streptococcal pharyngitis. The signs and symptoms that make up this syndrome are categorized between major and minor criteria (carditis, migratory arthritis, serologic assays, fever, etc.). The damage caused to endocardial tissue (in particular, the chronic scarring of heart valves) remains a major cause of morbidity worldwide, and is thought to result from molecular mimicry between the antigens of *S. pyogenes* and heart valve tissue.[1]

The definitive diagnosis of the invasive manifestations of *S. pyogenes* relies on culture of the organism from sterile sites. Throat cultures have traditionally been the gold

standard in the diagnosis of pharyngitis, but the delay in obtaining definitive results has led to the development of rapid antigen detection tests (RADT) that provide more immediate information.[2] This advent is particularly important when trying to differentiate streptococcal infections from viral upper respiratory infections that do not require antibiotics. When the organism is isolated from a lymph node abscess (as in this case), it is characterized on Gram stain as a Gram-positive coccus in short chains. When cultured on sheep's blood agar, it exhibits complete hemolysis and will produce elongated chains. Using the Lancefield classification system, it can be differentiated from other beta-hemolytic streptococci such as *Streptococcus agalactiae* (Group B streptococcus).[2–4]

## Management

*S. pyogenes* remains universally susceptible to penicillin, but rates of resistance to macrolides have emerged as a cause of concern, given the widespread use of these antimicrobials.[5] The pyogenic nature of the organism may lead to peritonsillar or lymph node abscess formation, a condition that may require surgical drainage to prevent occlusion of the airway. Necrotizing fasciitis is another manifestation that requires emergent surgical debridement in order to stop the massive destruction of tissues, as well as the massive cytokine release caused by nonspecific T-cell activation.[3] Nonsuppurative complications of *S. pyogenes,* such as glomerulonephritis, may be self-limiting; however, children with this syndrome should be treated with antibiotics to prevent spread of nephritogenic strains. The inflammation induced by acute rheumatic fever is treated with salicylates and corticosteroids, but continuous monthly injections of penicillin are used to prevent relapses.[1]

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## Sore Throat and Shortness of Breath followed by Septic Shock in a Healthy 18-Year-Old Polo Player

**Chapter:** Sore Throat and Shortness of Breath followed by Septic Shock in a Healthy 18-Year-Old Polo Player
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

An 18-year-old female college student with no past medical history presented to the emergency department in April with fever and shortness of breath. She played on the university polo team, and had been performing well in her classes. Seven days prior to admission, she reported to her friend and her sister that she had a sore throat and felt ill. She developed subjective fevers and shaking chills. A rapid streptococcal test was negative, and she received azithromycin from her student health facility without improvement. Over the 36 hours prior to admission, she experienced progressive shortness of breath and was admitted to her local community hospital with a chest radiograph showing bilateral pulmonary infiltrates, elevated bands (30%), and hypotension requiring vasopressor support. Blood cultures were drawn and she was started subsequently on vancomycin and cefepime. Her respiratory status deteriorated, requiring endotracheal intubation, and she was then transferred to our facility. Per the patient's family, she had no potential exposures other than cleaning horse stalls. She was not sexually active and had never used illicit drugs.

On transfer, rectal temperature was 38.6°C, blood pressure was supported on norepinephrine, and her respiratory function was supported on assist control ventilation with a fractional inspired oxygen concentration of 50%. She was responsive to voice but sedated. There was no cervical edema or lymphadenopathy, but she had a jugular venous wave 3cm above the sternal angle. There was no organomegaly, but trace lower extremity edema was present.

Her laboratory findings included anemia (hematocrit 26.7), and thrombocytopenia (platelets 55,000/mm$^3$, decreased from 122,000 on the day of admission), with normal white blood cell count (5000/µl). Other laboratory test findings were normal, including coagulation profile, HIV serology, urine Legionella antigen, and influenza PCR and transthoracic echocardiography.

Ciprofloxacin and doxycycline were added to her antimicrobial regimen. On the day after transfer, blood cultures from the outside facility were growing a Gram-negative rod in the anaerobic samples that was later identified as *Fusobacterium necrophorum* (Figures **5c.1a** and **b**). Computed tomography showed a left, nonocclusive, internal jugular vein thrombus (Figures **5c.2a and b**). On further questioning of the family, she had been complaining of left-sided neck pain prior to her respiratory decompensation. She was treated with metronidazole for 6 weeks, with complete resolution of symptoms and no long-term sequelae.





Figure 5c.1a
Blood agar plate revealing growth only under anaerobic conditions.



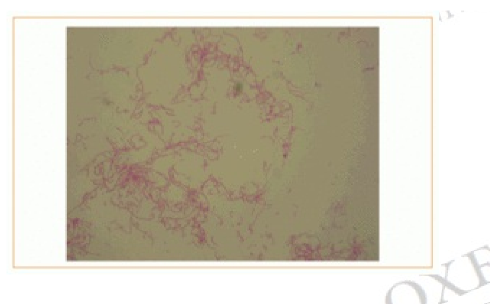




Figure 5c.1b
Gram stain of colonies with elongated Gram-negative bacilli.

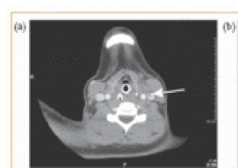




Figure 5c.2
(a) CT neck, transverse view revealing nonocculsive left internal jugular vein thrombosis; and (b) CT neck, coronal view revealing nonocculsive left internal jugular vein thrombosis.

**Case 5c Discussion: Lemierre's Syndrome**

## Clinical Features

Lemierre's syndrome was first described in 1936 as "suppurative thrombophlebitis of the internal jugular vein with metastatic infection." The syndrome is a complication of oropharyngeal infections, and since the initial description, the incidence has decreased due to the use of antibiotics for treatment of pharyngitis. The syndrome occurs almost exclusively in adolescents and young adults, with an estimated annual incidence of 14 cases per million adolescents.[1,2] *Fusobacterium necrophorum* is the etiologic agent in 81% of cases, and growth of this organism in blood cultures is nearly pathognomonic for this disease. Anaerobic streptococci, *Bacteroides*, and *Peptostreptococcus* have also been isolated in the setting of Lemierre's syndrome.

The diagnosis is often not considered due to the nonspecific initial clinical presentation. In an estimated 87% of cases, the syndrome occurs in association with pharyngitis,[3] but infection may originate from other sources in the head and neck. A patient may report symptoms of pharyngitis, upper respiratory tract symptoms, dysphagia, or dysphonia. Approximately 3–7 days after oropharyngeal symptoms start, there may be a slight improvement followed by the development of shaking chills and fever.[4] Swelling or pain in the neck can occur ipsilateral to the thrombosis and should suggest the diagnosis. Embolic or disseminated infection is often considered part of the definition of Lemierre's syndrome, and is present in up to 97% of patients with septic jugular thrombophlebitis. The lung is the most common site of metastatic infection (Figures **5c.3a and b**) and septic arthritis has been frequently reported. Severe sepsis, as in the case above, can occur. Although mortality has decreased since the initial description of the syndrome, 10% of patients exhibit persistent deficits after treatment.

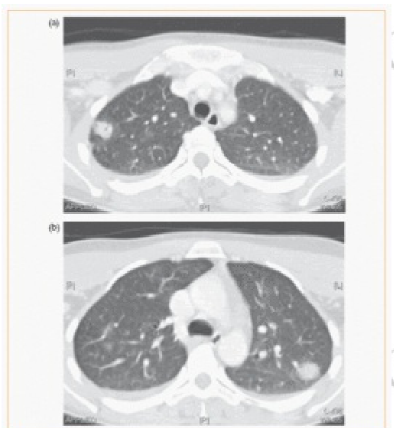






Figure 5c.3a and 3b
CT lungs axial view with bilateral upper lobe nodules. The right upper lobe nodule shows early cavitation consistent with septic pulmonary emboli.

## Diagnosis and Treatment

Diagnosis is made by radiologic identification—by computed tomography, ultrasound or MRI[5]—of jugular venous thrombus in conjunction with clinical and microbiologic data. Imaging often identifies pulmonary emboli with cavitation and pleural effusions. Parapharyngeal infection may not be evident on imaging, but edema surrounding the affected vein is common. The associated organism is generally identified through blood culture, and a sample taken from seeded tissue may also assist in the diagnosis.

Even in cases of multiorgan involvement, medical management with 3–6 weeks of antibiotics is generally effective. If Lemierre's syndrome is suspected, empiric antibiotic therapy should include a β-lactam antibiotic with an agent active against oral anaerobic bacteria. Ampicillin/sulbactam or ceftriaxone with clindamycin would be appropriate empiric regimens. Because some *Fusobacteria* produce a β-lactamase,[6] these regimens could also be used in the case of *F. necrophorum* infection until the presence of a β-lactamase has been excluded. Intravenous penicillin G should be used for treatment of β-lactamase negative *F. necorphorum,* and metronidazole is probably equally effective.

Macrolides and azithromycin are not clinically effective. The therapeutic benefit of anticoagulation and venous ligation is not well defined.

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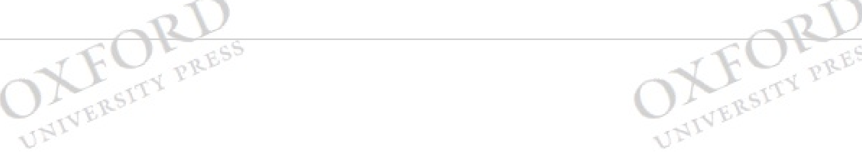
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## A Renal Transplant Recipient with Facial Pain and Swelling

**Chapter:** A Renal Transplant Recipient with Facial Pain and Swelling
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 77-year-old man with a history of an uncomplicated cadaveric kidney transplantation 5 months earlier for diabetic nephropathy presented with left-sided facial pain and swelling. He had previously consulted a dentist for dental pain and was prescribed penicillin without relief. The pain was severe over the left frontal, maxillary, and nasal sinuses, and radiated to the left temporal area. Immunosuppressive medications included tacrolimus, prednisone, and mycophenolate mofetil.

The patient was initially evaluated at an outside hospital, and was found to have a new facial nerve palsy. He was afebrile and normotensive, but violaceous, echymotic areas on his face were noted to be spreading (Figure **5d.1**). Initial laboratory values were significant for hyponatremia (sodium, 128 meq/L), acidosis (C02 19 meq/L) and hyperglycemia (glucose 161 mg/dl). His mental status progressively declined and he was intubated for airway protection shortly after transfer to our hospital. The patient's ophthalmologic examination was significant for proptosis, anisocoria with a fixed and dilated left pupil, and papilledema.



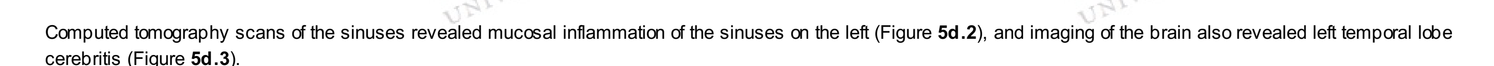



Figure 5d.1
Physical examination with marked facial swelling and violaceous and echymotic skin changes on the left side of the face.

Computed tomography scans of the sinuses revealed mucosal inflammation of the sinuses on the left (Figure **5d.2**), and imaging of the brain also revealed left temporal lobe cerebritis (Figure **5d.3**).

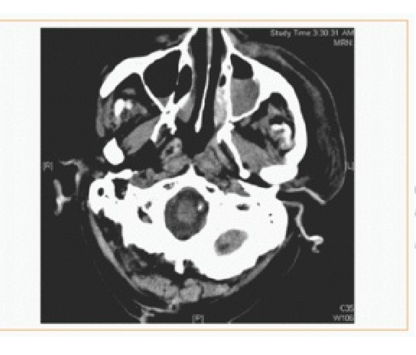





Figure 5d.2
CT scan sinuses, axial view with marked facial edema and left sided sinusitis with mucosal edema and air fluid levels.

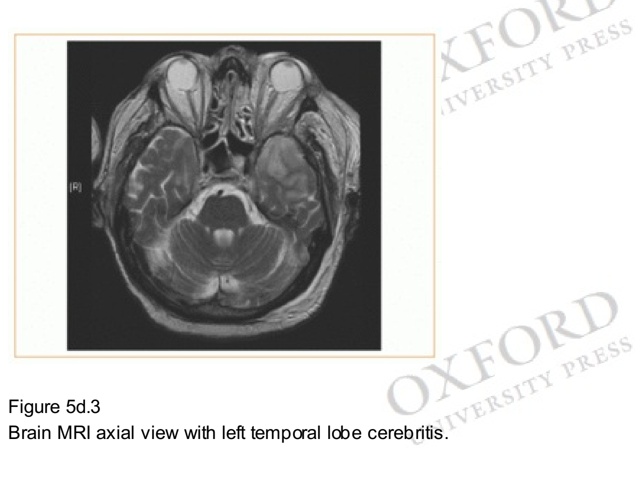


Figure 5d.3
Brain MRI axial view with left temporal lobe cerebritis.

Surgical debridement revealed that the mucosa of the nasal sinus cavity was boggy, edematous, and hemorrhagic. On the floor of the nasal cavity, filamentous material consistent with a fungus was seen by the surgeon. On pathologic examination, broad, ribbon-like fungal hyphae were seen on permanent sections stained with hemotoxylin-eosin (Figure **5d.4**) and Gomori methanmine silver stain (Figure **5d.5**). The hyphal elements were aseptate, branching at right angles, and invading blood vessels.

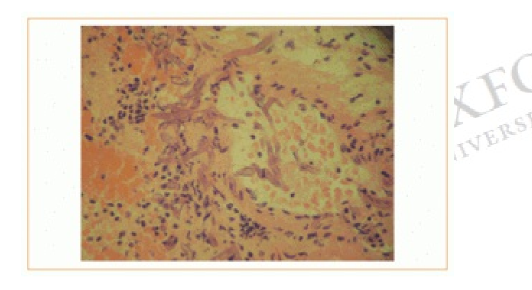
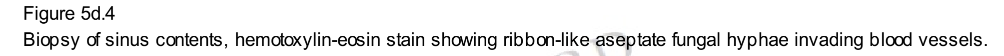


Figure 5d.4
Biopsy of sinus contents, hemotoxylin-eosin stain showing ribbon-like aseptate fungal hyphae invading blood vessels.



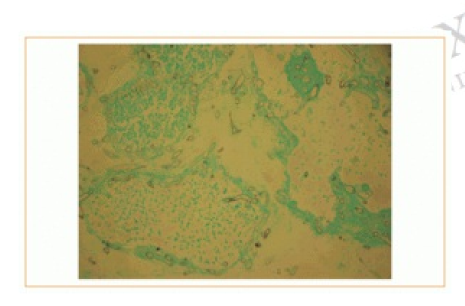


Figure 5d.5
Biopsy of sinus contents, Gomori methanmine silver stain with aseptate hyphae branching at right angles and invading blood vessels.

After several days of incubation, cultures of the nasal biopsied material began growing a mold that was subsequently identified as a *Rhizomucor* species (Figures **5d.6** and **5d.7**). The patient's course was further complicated by intracerebral extension of the infection, and infarction into the left middle cerebral artery territory. A decision to pursue only palliative measures was made, and the patient died shortly thereafter.

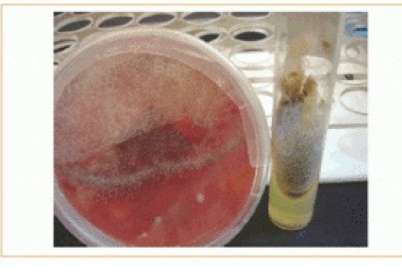




Figure 5d.6
Cultures of sinus contents on blood agar and Sabaroud's dextrose agar growing a mold identified as a a *Rhizomucor* species.

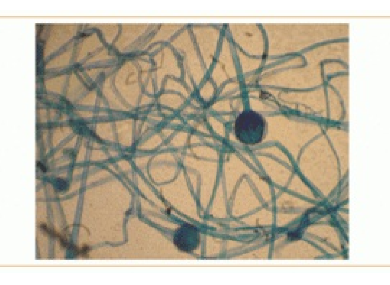






Figure 5d.7
Lactophenol stain of cultured material identified as a *Rhizomucor* species with large round sporangia.

**Case 5d Discussion: Mucormycosis**

## Epidemiology

Rhinocerebral mucormycosis is a devastating fungal infection that is often fatal in immunocompromised patients. The infection is caused by a group of molds that are characterized by broad, ribbon-like, aseptate or poorly-septated hyphae. Multiple genera and species were included in the class Zygomycetes, but this class has subsequently been renamed Glomeromycetes.[1] Due to this taxonomic reorganization, and the diversity of molds that can cause this invasive infection, the group is now referred to as the *agents of* mucormycosis.[1] Among the agents of mucormycosis, *Rhizopus* and *Rhizomucor* are among the most frequently isolated genera. These molds are environmental saprophytes and are widely found in environmental sources. They become invasive pathogens principally in immunocompromised hosts, particularly diabetics, neutropenic patients, organ transplant recipients, and patients receiving chronic corticosteroid therapy.[1]

Patients with diabetes mellitus are at increased risk for this infection due to a combination of factors: hyperglycemia leads to neutrophil dysfunction, and metabolic acidosis from diabetic ketoacidosis increases the availability of free iron, an important fungal growth factor. Iron overload in patients with hemochromatosis also increases their risk for invasive mucormycosis. Paradoxically, iron chelation therapy with deferoxamine also increases their risk, because it is used by the mold as a siderophore to increase intracellular iron uptake.[2] Modern iron chelators, such as deferasirox, are not associated with this property and have been shown to be protective in animal models of mucormycosis.[1] Prolonged neutropenia in the setting of cancer chemotherapy and hematopoietic stem cell transplantation has steadily increased in importance as a risk factor. Antifungal prophylaxis with voriconazole (which has activity against *Aspergillus*, but not against the agents of mucormycosis) has led to improved survival of patients with neutropenia, but the rate of non-*Aspergillus* mold infections has also been climbing.[3]

## Clinical Features and Diagnosis

Inhalation of fungal spores from the environment is the most common route of acquisition of the agents of mucormycosis. In the immunocompromised host with inadequate macrophage and neutrophil function, the spread of the organism is rapid and is not limited by soft tissues or bones. The angioinvasive nature of these molds leads to hemorrhage, thrombosis, and necrosis of local tissues. Sinus pain and swelling may be initially indistinguishable from bacterial causes of sinusitis, and radiographic findings are similarly nonspecific, showing inflammation of the sinus cavities with air-fluid levels and bony erosion. On physical examination, skin lesions may initially appear red or violaceous.[1] Later-stage angioinvasive infection may be detected by the presence of black, necrotic lesions that are visible in the nares, periorbital skin, or oral cavity. In immunocompromised patients, infections may progress from the nasal and sinus spaces to the brain in the course of a few days.[2]

Pulmonary infections with the agents of mucormycosis are difficult to distinguish radiographically from other invasive mold infections, and tissue biopsy and culture is generally required to confirm the diagnosis. Symptoms may include dyspnea, nonproductive cough, pleuritic chest pain, and fever. Computed tomography findings range from isolated cavitary nodules to diffuse bilateral infiltrates and wedge infarcts.[1] Gastrointestinal infection from ingested spores, and skin and soft tissue infections from direct inoculation, are manifestations of mucormycosis that may be seen in immunocompetent patients. Nonsterile bandages or dressings applied to surgical sites or traumatic wounds are a well-described source of cutaneous mucormycosis.[4]

The microscopic appearance of these molds in tissue often allows for their differentiation from other fungal organisms such as *Aspergillus*. The hyphae of the agents of mucormycosis are typically broad, ribbon-like, and lack septations, while those of *Aspergillus* species are thinner and divided by septations. The right-angle branching of the hyphae of the agents of mucormycosis also helps to differentiate them from the acute-angle branching of *Aspergillus* hyphae. Both molds may be visible on hematoxylin and eosin stained tissue, but Gomori methenamine silver stain enhances the visibility of the hyphae. Cultures of biopsied tissue allow for species identification, but they are rarely recovered from blood culture.[1,2] Agents of mucormycosis such as *Rhizopus* species grow well on standard blood agar and Sabouraud dextrose agar. They tend to grow more rapidly on culture media than *Aspergillus* species, and structures such as sporangia, columellae, and rhizoids allow for their differentiation.[2]

## Management

Due to its rapidly progressive nature in immunocompromised hosts, rhinocerebral mucormycosis represents a surgical and medical emergency. The importance of surgical debridement in upper airway disease is especially critical due to the anatomic proximity of the brain and the angioinvasive nature of the mold.[1] The primary antifungal medication used in conjunction with surgical debridement is amphotericin (deoxycholate and lipid preparations).[3,5] Lipid formulations of amphotericin are less likely to cause nephrotoxicity than nonlipid formulations, an attribute that is especially important in treating diabetic patients who may have underlying renal dysfunction.[1] While voriconazole has excellent activity against *Aspergillus* species, it lacks activity against the agents of mucormycosis. Therefore, rapid differentiation between *Aspergillus* and the agents of mucormycosis in pathologic tissues is essential in patients being treated empirically with voriconazole. With increasing use of voriconazole and echinocandins as routine prophylactic or presumptive therapy of neutropenic fever, the incidence of mucormycosis has increased in some cancer centers.[3]

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 27-Year-Old Woman with a Fever, Cough, and Pleuritic Chest Pain

**Chapter:** A 27-Year-Old Woman with a Fever, Cough, and Pleuritic Chest Pain
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 27-year-old woman with a history of scoliosis was admitted to the hospital with fever, worsening dyspnea, and nonproductive cough. Her initial symptoms began 4 days prior to admission with fever (eventually as high as 105° Fahrenheit), dry cough, left-sided pleuritic chest pain, and worsening dyspnea. In addition, she noted myalgias, headache, and diarrhea. She had been evaluated at a local pharmacy 2 days prior, where she had a negative rapid influenza test and had been told she most likely had a viral upper respiratory infection.

In the emergency department, she was in respiratory distress and spoke in short sentences. She was initially afebrile but tachycardic (pulse 144 beats per minute), extremely tachypneic (respiratory rate 37–54 breaths per minute), and hypoxic (oxygen saturation 84% on ambient air). The lowest blood pressure recorded was 114/65, and markedly decreased breath sounds were noted on auscultation of the left hemithorax. Her respiratory status rapidly declined, and she required endotracheal intubation and mechanical ventilatory support.

Her laboratory values were significant for leukocytosis (white blood cell count 22,700 per cubic milliliter) with a predominance of immature neutrophils (45% bands, 53% segmented neutrophils). Chest radiography revealed extensive bilateral infiltrates much worse on the left than the right (Figure **6a.1**). Computed tomography of the lungs confirmed the extensive bilateral infiltrates with air bronchograms (Figure **6a.2**).

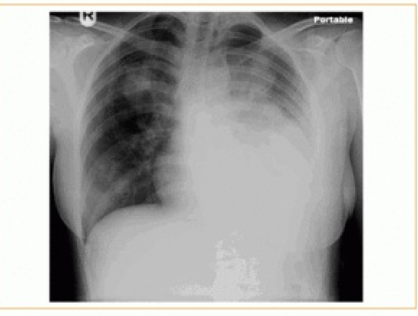





Figure 6a.1
Chest radiography revealed extensive bilateral infiltrates much worse on the left than the right.





Figure 6a.2
CT lungs with dense bilateral consolidations with air bronchograms.

Blood cultures became positive after 13 hours of incubation. The Gram stain from the aerobic bottle revealed Gram-positive cocci in pairs and chains (Figure **6a.3**). The Gram stain of anaerobic bottle was reported as Gram-positive cocci in pairs and Gram-negative rods (Figure **6a.4**).

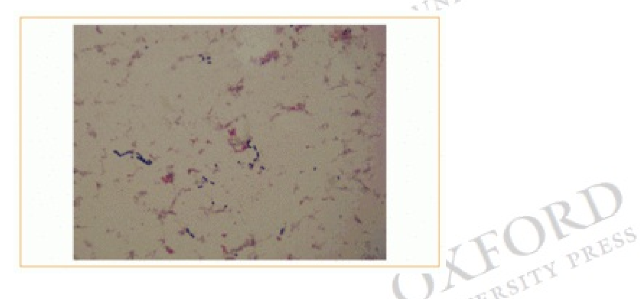




Figure 6a.3
Blood culture Gram stain from the aerobic bottle revealed Gram-positive cocci in pairs and chains.

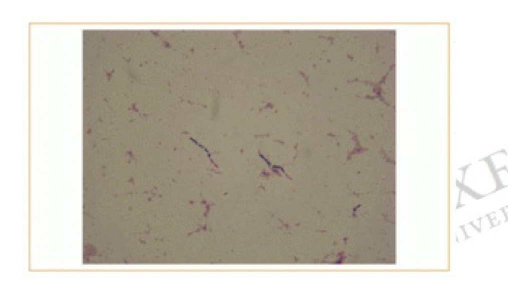


Figure 6a.4
Blood culture Gram stain of anaerobic bottle was reported as Gram positive cocci in pairs and Gram-negative bacilli. The elongated Gram-negative appearance of the organism was an artefact likely caused by autolysis.

The patient was treated with ceftriaxone and azithromycin, as well as with metronidazole, given the apparent polymicrobial bacteremia with Gram-positive cocci and anaerobic Gram negative-bacilli. A pleural fluid sample re-vealed turbid fluid with 10,430 white blood cells per microliter (52% poly-morphonuclear cells, 32% macrophages), 3200 red blood cells, pH 7.7, lactate dehydrogenase 2549, and protein ( 2gm/dl. A chest tube was placed both for the empyema and for the pneumothorax that resulted from the thoracentesis. Cultures of the pleural fluid remained sterile.

Eventually, the only organism identified from the blood cultures was penicillin-susceptible *Streptococcus pneumoniae* (minimal inhibitory concentration ( 0.03 micrograms/ml) (Figure **6a.5**). The gram negative appearance of the organisms was an artefact most likely caused by pneumococcal autolysis. The patient was soon extubated and eventually discharged from the hospital with a full recovery after a total of 4 weeks of anti-pneumococcal antibiotics (ceftriaxone and then amoxicillin). She was sub-sequently evaluated for possible immunodeficiency, given the severity of her illness, but none was found.

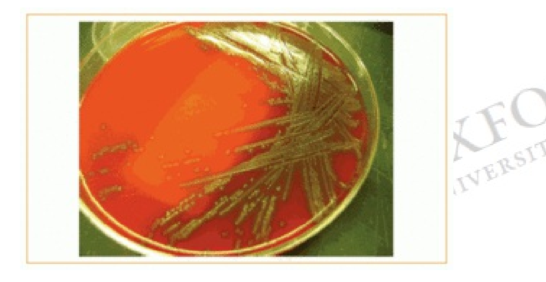




Figure 6a.5
Blood agar plate showing alpha hemolytic colonies of *Streptococcus pneumoniae.*



**Case 6a Discussion: *Streptococcus pneumoniae***

## Diagnosis and Clinical Features

*Streptococcus pneumoniae,* or pneumococcus, is the leading cause of community-acquired pneumonia (CAP) worldwide. The overall rate of CAP ranges from 8–15 per 1000 persons per year. In the United States, common serotypes associated with invasive disease include 4, 6B, 19, 18C, 23 and 9V as well as 3. Clinical features of pneumococcal pneumonia include acute fever, chills, productive cough, dyspnea, and leukocytosis with predominance of neutrophils. Definitive diagnosis is sometimes difficult, as the organism is only isolated in blood culture in 5%–18% of cases.[1] Attempts to culture blood, sputum, deep tracheal aspirates, and pleural fluid—particularly in the case of a parapneumonic effusion or empyema—should be made. Once *Streptococcus pneumoniae* is identified by culture, it can be separated from other streptococcal species by its pattern of hemolysis, its sensitivity to optochin, and its lysis by bile salts.[2] Gram staining of the organism usually reveals Gram-positive lancet-shaped diplococci; however, autolysis may cause the organism to appear elongated and Gram-negative, as in the above case.[2] The initial finding of “polymicrobial” bacteremia prompted concern for the possibility of aspiration pneumonia or acute respiratory distress syndrome (ARDS) in response to a perforated esophagus.

Other, more rapid tests for the identification of pneumococcus include the detection of pneumococcal antigen, particularly in urine and CSF, as well as real-time polymerase chain reaction (PCR) to detect pneumolysin and hemolysin. The sensitivity of the urine pneumococcal antigen has been reported to be about 80% with a specificity close to 98%; however, other studies have shown healthy asymptomatic carriers of pneumococcus to be positive with the urine antigen as well, raising issues of its overall utility in

clinical practice.[3,4]

The pneumonia severity index (PSI) is one of the most widely used and validated scoring systems for predicting mortality risk and aiding clinicians in the decision to admit a patient with CAP. Because it is composed of 20 variables, it may be cumbersome as a practical clinical tool. As a result, other, simpler scoring systems have been developed, such as the CURB-65 and the severity community-acquired pneumonia (SCAP) score. The former is calculated based on 5 variables, and the latter on 2 major and 6 minor criteria.[5–7]

## Treatment and Prevention

Because of emerging penicillin resistance in pneumococcal isolates worldwide, empiric treatment for CAP consists of a third-generation cephalosporin such as ceftriaxone, plus a macrolide antibiotic. Patients with pneumococcal pneumonia susceptible to penicillin may be treated with penicillin, once susceptibility is confirmed. Those with high level penicillin resistance may be treated with a third-generation cephalosporin (if susceptible), or with vancomycin, and should be treated at least 5 days beyond clinical resolution.[8]

Three vaccines currently exist for the prevention of *S. pneumoniae*: two conjugate vaccines and one unconjugated polysaccharide vaccine. The heptavalent pneumococcal conjugate vaccine (PCV-7), which contains the 7 capsular polysaccharides most commonly involved in pediatric infections is being superseded by the 13-valent conjugate vaccine (PCV-13), which contains protection against an additional 6 strains. The 23-valent pneumococcal polysaccharide vaccine is used in adults and older children with specific conditions that increase their risk of invasive pneumococcal disease. The conjugate vaccines (PCV-7 and PCV-13) induce a mucosal immune response in immunized individuals which results in eradication of colonizing pneumococci of the vaccine serotypes.[8–10]

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## A 31-Year-Old Man with Skin Lesions Following a Respiratory Illness

**Chapter:** A 31-Year-Old Man with Skin Lesions Following a Respiratory Illness
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### Case Presentation

A 31-year-old man with a past history of genital herpes presented with painful oral ulcers and vesicles on his lips, extremities, and genitals. He had taken valacyclovir when he first noted the genital lesions, but in the past he had never had oral lesions. Two weeks prior to presentation he had experienced fevers, night sweats, and cough productive of bloody sputum that had resolved after taking azithromycin for 5 days.

On physical examination he appeared uncomfortable but in no acute distress. He was febrile to 100.3°F. and had numerous vesicles on the lips, extremities, and genitalia (Figures **6b.1** and **6b.2**). His conjunctivae had no abnormalities, but there were ulcerated lesions on his hard palate. Other than the dermatologic and mucosal findings, the rest of his physical examination was unremarkable. Chest radiography revealed prominent hila, but no focal consolidations (Figure **6b.3**). Scraping of the ulcers and unroofed vesicles were negative for HSV, and VZV antigens were negative by direct fluorescent antibody and viral culture. A skin biopsy revealed necrotic keratinocytes at all levels of the dermis, as well as a perivascular mononuclear infiltrate, confirming the diagnosis of erythema multiforme major. The patient's *Mycoplasma pneumoniae* IgM and IgG (282 units) were both positive. Because of the severity of the mucosal involvement, the patient was treated with oral prednisone, and the lesions resolved after 10 days.





Figure 6b.1
Vesicular lesions on the lips.





Figure 6b.2
Vesicular lesions on the lower extremities.





Figure 6b.3
Chest radiograph, anterior-posterior view with prominent hila but no focal consolidations.

**Case 6b Discussion: *Mycoplasma pneumoniae***

## Microbiology and Epidemiology

*M. pneumoniae* is a small (about 10 x 200 nm) prokaryote, with an organelle at one end containing major adhesion proteins that allow attachment to cell membranes and give the organism an affinity for respiratory epithelium. It lacks a cell wall, instead possessing a sterol-containing outer trilaminar membrane. The lack of a peptidoglycan cell wall makes the organism invisible on Gram stain and inherently resistant to beta-lactam antibiotics. *M. pneumoniae* is a fastidious organism that reproduces by binary fission with a doubling time of more than six hours.[1]

*M. pneumoniae* is an extracellular parasite that initiates infection by attaching to ciliated respiratory epithelium with the aforementioned terminal organelle. Upon infection, ciliary action ceases and is followed by loss of cilia and desquamation of the effected epithelial cells—a likely cause of the intractable cough that is a frequent symptom of the disease. Hydrogen peroxide, which is elaborated by the organism, may cause in vivo cellular damage, and is the cause of the hemolysis exhibited by colonies growing on blood agar plates.[2] *M. pneumoniae* actively stimulates the immune system, resulting in the production of numerous proinflammatory and anti-inflammatory cytokines. It also cause the production of numerous antibodies, some of which appear to have some neutralizing ability, but others appearing to be autoantibodies, with the best studied being the cold agglutinins.[3]

*M. pneumoniae* is spread by respiratory droplets produced by coughing; typically close contact with the index is required for transmission. Infection usually occurs singly or as family outbreaks (the index case frequently being a child), though mini-epidemics can occur in closed populations (e.g., military barracks, boarding schools).[4] The annual incidence of mycoplasma pneumonia in the United States is estimated to be one case per 1000 persons (approximately 2 million cases annually), though the incidence of non-pneumonic *Mycoplasma* respiratory disease is thought to be much higher.[5] Disease can occur at any age, but the highest attack rates occur in those between the ages of 5 and 20. *M. pneumoniae* has a worldwide distribution, and most studies do not show a seasonal pattern to infection, though many out-breaks tend to occur during the fall months when other causes of community-acquired pneumonia are less common.[3]

## Clinical Features

Most episodes of infection affect the upper respiratory tract and result in clinically apparent disease. The incubation period is between 2 and 3 weeks, and is followed by the insidious onset of fever, malaise, headache, and cough (Figure **6b.4**). The cough, which is usually nonproductive but can be associated with white or blood-flecked sputum, tends to increase in intensity and frequency over the course of 1–2 weeks and can become debilitating. The disease may progress to tracheobronchitis or pneumonia in a small percentage of patients, in which case the cough can become more severe and associated with chest pain or soreness from muscle strain; true pleuritic chest pain is uncommon. Fever can be present, but shaking chills or rigors are uncommon. In contrast to viruses that can cause an atypical pneumonia, such as influenza or adenoviruses, infection with *M. pneumoniae* is rarely associated with gastrointestinal complaints or myalgias.[3]

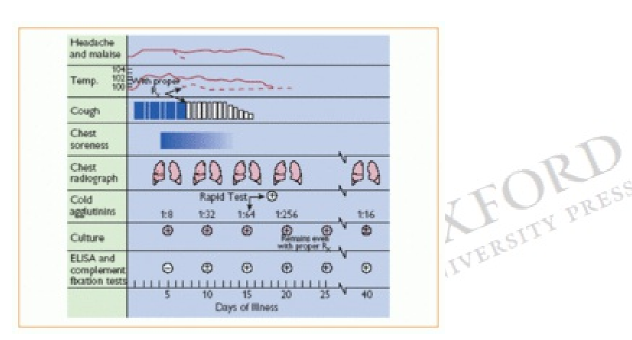





Figure 6b.4
Major clinical and laboratory manifestations of mycoplasmal pneumonia. ELiSA, enzyme-linked immunosorbent assay. This figure was published in Baum SG. *Mycoplasma pneumoniae* and Atypical Pneumonia. In: Mandell GL, Bennett JE, Dolin R eds. *Mandell, Douglas, and Bennett's Principles and Practice of infectious Diseases*, 7th ed. p.2481–2489. Copyright Elsevier 2009.

On physical examination, pharyngeal erythema may be present but is usually not associated with extensive cervical lymphadenopathy, as is frequently the case with Group A streptococcal pharyngitis.[3] Bullous myringitis is occasionally seen, but can be associated with viral infections as well; its presence or absence is not sufficient to establish or exclude infection.[3] Chest examination is frequently unrevealing, and rarely will patients have significant rales or percussive findings, although wheezing can occur. Patients' radiographic findings are generally more impressive than the patient's appearance or objective findings on physical exam; hence the term, "walking pneumonia."

Infection with *M. pneumoniae* tends to be mild and self-limited, though severe manifestations and even death have been reported in patients with sickle cell disease or other sickle cell related hemaglobinopathies. The effect of other types of immune deficiencies, in particular, HIV infection, on disease severity is unclear. Extrapulmonary findings in a wide variety of organ system have been reported, including cardiac (congestive heart failure, conduction abnormalities, arrhythmias), musculoskeletal (polyarthralgias), and neurologic (encephalitis, meningoencephalitis, aseptic meningitis, Guillain-Barré syndrome) manifestations. Dermatologic manifestations, however, are the most common extrapulmonary site of disease.

Erythema multiforme (EM) or Steven-Johnson syndrome occurs in approximately 7% of cases with the majority of cases occurring in young males. The classic appearance of

EM lesions are erythematous circular lesions with central clearing (target lesions) distributed mainly on the extremities. Severe mucosal inflammation occurs with erythema multiforme major. The underlying pathogenesis of EM is poorly understood, but may be secondary to deposition of immune complexes in the superficial microvasculature of the skin. Management of erythema multiforme major with corticosteroids has been advocated, though evidence for this approach from controlled trials is lacking and most cases are self-limited.[5]

## Diagnosis

While isolation of *M. pneumoniae* is the gold standard for diagnosis, culturing the organism is an intricate and lengthy process requiring specialized media, and is rarely performed in most hospital and commercial laboratories. Instead, a diagnosis is usually made based on clinical features and serological tests. The cold agglutinin assay, once the mainstay of diagnosis, is neither sensitive nor specific and should not be used except as an adjunct to clinical judgment and other tests. A chest radiograph may reveal extensive pulmonary infiltrates that are out of proportion to objective physical findings and the patient's reported symptoms, though in practice, patients will often have a normal radiograph. The most frequently used tests are enzyme-linked immunoassays for *M. pneumoniae* specific IgM and IgG, with IgM being the most useful in detecting acute infection.[1] These assays are both sensitive and specific, but are frequently negative early in the course of infection and thus are not always useful in guiding initial therapy (see Figure **6b.4**). Ideally, acute and convalescent titers collected 2–3 weeks apart should be compared, with a fourfold increase in titers indicative of infection. Polymerase-chain reaction (PCR) assays have been shown to be both sensitive and specific, but are not widely available because of a lack of standardization of both the probe and the assay.[1]

## Treatment

Infection with *M. pneumoniae* is generally self-limited though treatment can shorten the duration and severity of symptoms. Macrolides, tetracyclines and respiratory flouroquinolones (e.g. levofloxacin and moxifloxacin) are effective against this intracellular pathogen, but cell wall acting agents (such as beta-lactam antibiotics) are ineffective since it lacks a cell wall. The macrolides, tetracycline and flouroquinolones are all effective against other bacterial causes of atypical pneumonia (e.g. *Legionella* spp., *Chlamydia pneumoniae*).[2]

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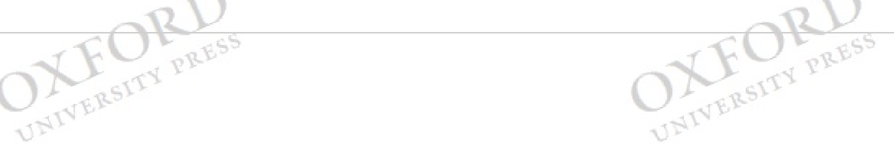
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## Persistent Cough in a Woman from Mexico

**Chapter:** Persistent Cough in a Woman from Mexico
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 29-year-old woman from Mexico presented to the emergency department on three occasions for persistent cough for several weeks. She was discharged on the first two visits with a diagnosis of atypical pneumonia, and treated initially with azithromycin. On the third visit, a Spanish interpreter better elucidated her symptoms, which included drenching night sweats, weight loss (13 pounds), and hemoptysis. The hemoptysis had initially been small amounts, but on the previous day she had been coughing much greater volumes of bright red blood and clots (Figure **6c.1**). She had been living in the United States for 12 years, and 5 years prior to admission her husband had been treated for pulmonary tuberculosis.





Figure 6c.1
Massive hemoptysis.

On physical examination, she was afebrile, with an oxygen saturation of 97% on ambient air, and crackles were present in the right upper lobe. A complete blood count revealed anemia (hemoglobin of 12.1 mg/dl) but normal white blood cell (10.1 × $10^3$ cells/μl) and platelet counts (356×$10^3$ cells/μl). Chest radiography revealed a right upper lobe infiltrate, and CT scan confirmed the presence of several upper lobe cavities as well as miliary nodules and hilar lymphadenopathy (Figures **6c.2**, **6c.3**, and **6c.4**). The first four sputum samples were negative for acid-fast bacilli, but a fifth specimen showed several organisms with a typical beaded, clumped appearance (Figure **6c.5**).





Figure 6c.2
Posterior-anterior chest radiograph showing right upper lobe cavity and increased interstitial markings.



Figure 6c.3
CT chest, axial view with multiple cavities and small nodules in the right upper lobe.

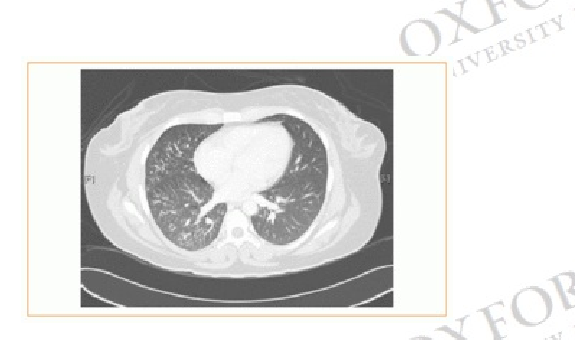


Figure 6c.4
CT chest, axial view with diffuse miliary nodules throughout the right hemithorax.

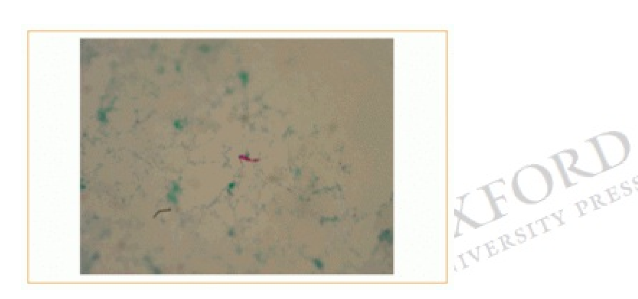




Figure 6c.5
Acid-fast stain of sputum sample showing clumps of beaded acid-fast bacilli.

Treatment with rifampin, isoniazid, pyrazinamide, and ethambutol was initiated, but the patient had an episode of massive hemoptysis and was intubated with a bifurcated endotracheal tube. The patient underwent embolization of a bronchial artery that was in direct communication with the largest cavity in the right upper lobe. The next day the endotracheal tube was removed, and smears of her sputum samples became negative for acid fast bacilli. Ten days later, sputum cultures collected on the day of admission grew *Mycobacterium tuberculosis* complex that was susceptible to all four medications. The patient was discharged with plans for a 6-month course of anti-TB medications under directly observed therapy (DOT).

**Case 6c Discussion: *Mycobacterium tuberculosis***

## Microbiology and Epidemiology

The *Mycobacterium tuberculosis* complex comprises seven species in the genus *Mycobacterium*, family Mycobacteriaceae, and order Actinomycetales, which are causes of human tuberculosis and zoonotic disease, with *M. tuberculosis* causing the vast majority of human infections. *Mycobacterium bovis*, a cause of disease in cattle, can be transmitted to humans via close contact with infected livestock or ingestion of unpasteurized dairy products; human-to-human transmission has been reported as well. *Mycobacterium africanum* and *Mycobacterium canetti* are both rare etiologies of tuberculosis in Africa. *Mycobacterium caprae*, *Mycobacterium microti*, and *Mycobacterium pinnipedii*—pathogens of cattle, rodents, and seals, respectively—have been reported to cause zoonotic tuberculosis (TB) in humans.[1]

TB is typically spread by aerosolized droplets containing tubercle bacilli, expectorated by patients with active pulmonary TB; rarely, primary inoculation occurs in non-pulmonary sites, such as abraded skin, the intestine, the oropharynx, or the genitalia (see Figure **6c.6**). These droplets are inhaled by susceptible individuals into the terminal alveoli, where an initial focus is formed and multiplication begins. The initial focus is frequently subpleural, and located in the midlung zone where airflow is greatest. Bacilli are subsequently carried by infected macrophages via the lymphatic system to regional lymph nodes or (particularly in non-immune persons) are transmitted hemato-genously throughout the body. Certain sites, including the lymph nodes, kidneys, epiphyses of the long bones, vertebral bodies, juxtaependymal meningeal areas adjacent to the subarachnoid space, and (most importantly) the apical-posterior areas of the lungs, favor bacillary multiplications; these sites can serve as a nidus of progressive infection, either immediately or after a variable period of latency.[1,2]

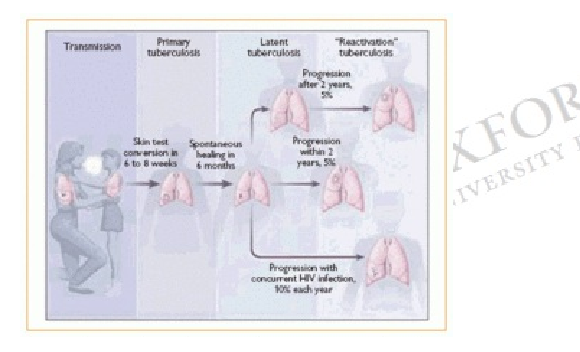






Figure 6c.6

Tuberculosis natural history and transmission. Reprinted with permission from Small PM, Fujiwara Pi. Management of tuberculosis in the United States. *New England Journal of Medicine* 2001;345(3):192–200.

In approximately 90% of hosts with intact cell-mediated immunity (antibodies are produced in response to infection but appear to play little role in the host defenses) the primary infection is controlled and latent infection is established, the clinical hallmark of which is a positive tuberculin skin test. Infection can reactivate months or years later (secondary or reactivated TB), manifesting in the areas of the body where latent infection has been established (see above)—most frequently, the apices of the lungs—and is most likely in the year following primary infection. Reactivation can occur spontaneously or as a result of weakening in the cell-mediated immunity of the host, associated with certain risk factors (Table 6c.1). In immunocompetent patients with latent TB, 5% will experience secondary tuberculosis within 2 years of primary infection and an additional 5% will have active disease at some later point in their lives. In patients with HIV infection, the rate of reactivated TB in those with latent infection is 10% per year; hence, tuberculosis is a major cause of morbidity and mortality in HIV infected patients from TB-endemic areas.[2] In the 10% of hosts who are unable to control the initial primary infection, replication continues, resulting in disseminated (miliary TB), extrapulmonary, or primary progressive disease. Those with deficits in cell-mediated immunity, particularly persons infected with HIV, are frequently unable to control the initial primary infection and will often present with primary progressive, extra-pulmonary or disseminated disease.[1]

| Table 6c.1 immunosuppressive conditions associated with reactivation of tuberculosis. While not an exhaustive list, these are the most frequent risk factors likely to be encountered by clinicians in practice |
|---|
| Diabetes Mellitus |
| End Stage Renal Disease |
| Old Age |
| immunosuppressive Drugs: (Particularly Corticosteroids, TNF alpha inhibitors) |
| Malignant Lymphoma |
| HiV infection/AiDS |

A total of 12,898 cases of TB were reported in the United States in 2008. This represents a decline of 3.8% from 2007 to 4.2 cases per 100,000 population, the lowest rate recorded since national reporting began in 1953 (Figure **6c.7**). A majority of cases were among foreign-born persons: among persons whose country of origin was known, approximately 95% of Asians, 76% of Hispanics, 32% of blacks, and 18% of whites were foreign born. In the U.S.-born, the greatest racial/ethnic disparity was in blacks, who had a rate seven times that of U.S.-born whites.[3] Worldwide, 9.27 million new cases of TB occurred in 2007 with an incidence of 139 per 100,000 persons.[4]

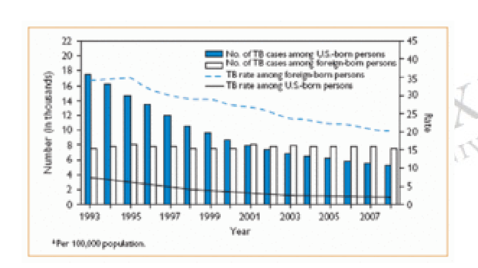






Figure 6c.7

Tuberculosis epidemiology. *Source*: Centers for Disease Control and Prevention. Trends in Tuberculosis – United States 2008. *MMWR* 2009;58:252.

## Clinical Features

Given its tendency to cause disease in virtually any organ system, TB infection frequently has a protean presentation, particularly in extra-pulmonary TB, where symptoms are often related to the organ system affected (see Chapters 1, 8, and 12). The signs and symptoms of TB are frequently subtle and nonspecific; a high level of clinical suspicion based on knowledge of risk factors and local epidemiology is necessary to diagnose this disease.

Pulmonary TB, particularly secondary TB, presents insidiously. Fever, often accompanied by night sweats, weight loss, and fatigue, are the most common symptoms; in many cases, constitutional complaints are the sole presenting symptoms. Cough is more frequent in secondary TB compared to primary TB, and is often mild and nonproductive initially, but as the disease progresses the cough can become more severe and productive of mucus, particularly in the morning when secretions are at their greatest. Hemoptysis can manifest later in the course of the disease, and is usually a result of endobronchial disease or cavitation/necrosis; hemoptysis is not necessarily indicative of active disease, and its presence or absence is not particularly helpful in the diagnosis of pulmonary TB. Life-threatening hemoptysis may occur when cavities communicate with bronchial or pulmonary arteries (Rasmussen's aneurysm), and may require embolization or surgical resection in severe cases. Dyspnea may also be present when there

is extensive lung involvement, pleural effusion, or pneumothorax. Pleuritic chest pain is uncommon, but when present may indicate pleural or pericardial involvement.

Physical findings are subtle and frequently absent unless the patient presents with advanced or severe disease. Amphora or absent breath sounds may be heard over areas of cavitation. Rales may be present through inspiration or after a cough (post-tussive rales). Dullness to percussion or decreased tactile fremitus are present in cases of pleural thickening or effusion.[1] Persons with HIV frequently have atypical or more acute presentations of TB than non-HIV-infected patients; the diagnosis of TB should be considered in any patient infected with HIV who presents with pulmonary complaints.

## Diagnosis

The diagnosis of TB is primarily based on isolating the organism whenever possible. Not only does this confirm the diagnosis, but it also allows for drug-susceptibility testing—an important issue in an era of rising drug resistance. In cases of suspected extrapulmonary tuberculosis, isolation of the organism from otherwise sterile sites or tissue samples is critical, given the often nonspecific signs and symptoms of extrapulmonary TB and the broad differential diagnosis. Invasive procedures to collect adequate tissue specimens may be necessary in these cases.

Staining for acid-fast bacilli (AFB) on expectorated sputum is the initial diagnostic test for pulmonary TB. A minimum of three sputum samples should be collected, with at least one collected in the early morning when the yield is highest. Patients who cannot provide sputum should undergo sputum induction. A positive smear provides strong support for the diagnosis of TB, but should be confirmed via cultures or nucleic acid amplification assays (NAAT). Bronchoscopy is not recommended unless other methods for acquiring sputum are ineffective, sputum testing is inconclusive, or another diagnosis is being entertained. In most studies, bronchoscopy does not appear to have diagnostic superiority when compared to sputum induction, and carries a higher risk of nosocomial transmission to healthcare workers.[1]

Sputum smears may be negative in patients with active pulmonary TB, particularly in patients with HIV or those without cavitary disease. In these cases, sputum culture is sensitive and specific, underscoring the importance of collecting samples for culture in all patients suspected of having TB. All patients suspected of having TB should undergo HIV testing as soon as the diagnosis is entertained.

## Treatment

The treatment of TB benefits the patient by curing a life-threatening disease, and the community benefits by preventing the transmission of a contagious, deadly infection. As such, physicians take on a public health role which carries the responsibility of appropriately prescribing an effective antimicrobial regimen and ensuring patient adherence to treatment. Management of TB should be performed in conjunction with local departments of health under DOT. An adherence plan, based on an assessment of medical, social, and economic barriers to adherence, should be implemented at the same time treatment is started.

While there are clear guidelines on the treatment of drug-susceptible TB, clinicians with little experience in the management of TB should consider referring these patients to more knowledgeable practitioners. There are serious public health implications if treatment fails, or drug-resistant isolates are selected for by incorrectly prescribed regimens or patient nonadherence. The management of drug-resistant TB is beyond the scope of this discussion, and should only be performed with the help of experts with firsthand experience in the management of drug-resistant tuberculosis. Treatment should be initiated when the diagnosis of tuberculosis is confirmed microbiologically in patients who are smear negative, but where there is a strong clinical suspicion for TB and no other likely diagnosis, or in patients who are severely immunosuppressed and the diagnosis of TB is seriously considered.

The medications of choice for the treatment of TB are isoniazid, rifampin, pyrazinamide, and ethambutol. In most cases, initial treatment requires use of all four drugs for at least 2 months (intensive phase) followed by 4 months of treatment with rifampin and isoniazid (Table 6c.2). Ethambutol can be discontinued before the end of the intensive phase if susceptibility to all first-line drugs is confirmed. Streptomycin, an injectable drug that has been shown to be highly efficacious, is currently not recommended as initial treatment because of increasing global resistance to this drug, but it can be used in patients intolerant of ethambutol with documented streptomycin-susceptible isolates. Rifapentine, a long-acting rifamycin which can be given once weekly, can be used in lieu of rifampin during the continuation phase in HIV-negative patients with non-cavitary disease and negative AFB sputum smears after 2 months of treatment. Data is lacking supporting the use of rifapentine during the intensive phase or in patients with cavitary disease, and it should not be used for these purposes. Rifapentine is contraindicated in persons infected with HIV.[1]

Table 6c.2 Treatment of Pulmonary Tuberculosis

| Initial phase | | | Continuation phase | | | | Rating* (evidence)‡ | |
|---|---|---|---|---|---|---|---|---|
| Regimen | Drugs | interval and doses‡ (minimal duration) | Regimen | Drugs | Interval and doses§ (minimal duration) | Range of total doses (minimal duration) | HIV- | HIV+ |
| 1 | INH<br>RIF<br>PZA<br>EMB | Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶ | 1a<br>1b<br>1c** | INF/RIF<br>INH/RIF<br>INH/RPT | Seven days per week for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)¶<br>Twice weekly for 36 doses (18 wk)<br>Once weekly for 18 doses (18 wk) | 182–130 (26 wk)<br>92–76 (26 wk)<br>74–58 (26 wk) | A (I)<br>A (i)<br>B (i) | A (II)<br>A (ii)#<br>E (i) |
| 2 | INH<br>RiF<br>PZA<br>EMB | Seven days per week for 14 doses (2 wk), then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk),¶ then twice weekly for 12 doses (6 wk) | 2a<br>2b** | INH/RiF<br>INH/RPT | Twice weekly for 36 doses (18 wk)<br>Once weekly for 18 doses (18 wk) | 62–58 (26 wk)<br>44–40 (26 wk) | A (II)<br>B (I) | B (II)#<br>E (I) |
| 3 | INH<br>RIF<br>PZA<br>EMB | Three times weekly for 24 doses (8 wk) | 3a | INH/RIF | Three times weekly for 54 doses (18 wk) | 78 (26 wk) | B (I) | B (II) |
| 4 | INH<br>RIF<br>EMB | Seven days per week for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)¶ | 4a<br>4b | INH/RIF<br>INH/RIF | Seven days per week for 217 doses (31 wk) or 5 d/wk for 155 doses (31 wk)¶<br>Twice weekly for 62 doses (31 wk) | 273–195 (39 wk)<br>118–102 (39 wk) | C (I)<br>C (I) | C (II)<br>C (II) |

Definition of abbreviations: EMB = Ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

* **Ratings guide**:

**A** – Preferred (should generally be offered). **B** – Alternative (acceptable to offer). **C** – Offer when preferred or alternative regimens cannot be given. **D** – Should generally not be offered. **E** – Should never be offered.

**Quality of evidence supporting the recommendation**:

**I** – At least one properly randomized trial with clinical end points.

**II** – Clinical trials that either are not randomized or were conducted in other populations.

**III** – Expert opinion.

‡ When DOT is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be in effective practice.

§ Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31 week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

¶ Five-day-a-week administration is always given by DOT. Rating for 5 day/week regimens is AIII.

# Not recommended for HIV-infected patients with CD4+ cell counts <100 cells/µl.

** Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

*Source*: Centers for Disease Control and Prevention. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. MMWR. June 20,2003; 52(No. RR11): 1–77.

The continuation phase, in patients with drug-susceptible disease, should be extended to 7 months in three situations: (1) patients with cavitary disease with a positive sputum culture collected at 2 months of treatment; (2) those who did not receive pyrazinamide during the intensive phase; and (3) those receiving once weekly isoniazid and rifapentine during the intensive phase, who have a positive sputum culture collected at 2 months.

Sputum must be collected at a minimum of once a month until two consecutive specimens have negative cultures. Patients should also undergo clinical examination at least monthly, and questioned carefully for medication-related adverse events. Baseline laboratory testing of hepatic and renal function and platelet count should be collected prior to the initiation of treatment; routine laboratory monitoring of hepatic and renal function or platelet count is unnecessary after treatment is initiated, except in those with baseline abnormalities or risk factors for hepatotoxicity (e.g., viral hepatitis, alcoholism).[5] Patients who are culture-positive after 2 months of therapy should be carefully evaluated for reasons to explain poor response. Such reasons may include poor adherence, drug resistance, extensive cavitary disease, laboratory error, or malabsorption of medications.

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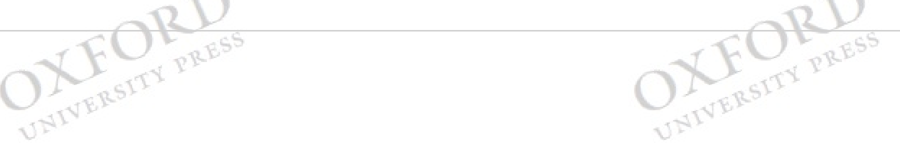
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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## Respiratory Distress in 2009

**Chapter:** Respiratory Distress in 2009
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**DOI:** 10.1093/med/9780199735006.003.0029

### Case Presentation

A 47-year-old female with a past medical history of anxiety, depression, and hypertension, presented to the emergency department in May 2009 with a 6-day history of malaise, cough, chills, and subjective fever. These symptoms had progressively worsened over the 3 days prior to presentation, during which there was also development of pleuritic chest pain and one episode of hemoptysis. Her daughter had encouraged her to seek medical attention sooner but she had declined. She reported that her grade-school-aged son had been sick with a sore throat, fever, rhinorrhea, and cough, the week before the onset of her symptoms.

Within a few hours of presentation to the ED, she developed increasing dyspnea, hypoxia (oxygen saturation 88% on room air), and hemodynamic instability (BP 60/45 mm Hg, HR 133 beats per minute) requiring in-tubation. On exam, coarse rales were present bilaterally. Notable laboratory findings included leucopenia (0.8 x $10^3$ WBC per µl), throm-bocytopenia (103 x $10^3$ platelets per µl), acute kidney injury (creatinine 2.9 mg/dl), and combined metabolic and respiratory acidosis (pH 7.02, pCO2 60 mm Hg, and lactic acid 13.2 mmol/L). Chest radiograph revealed a right upper lobe consolidation with air bronchograms (Figure **6d.1**).

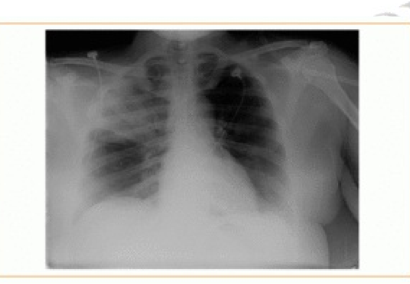


Figure 6d.1
Chest radiograph, posterior-anterior view revealed a right upper lobe consolidation with air bronchograms.

The patient was treated with vancomycin, cefepime, levofloxacin, oseltamivir, and vasopressors, and transferred to the ICU. She remained critically ill, experienced four cardiac arrests, and expired within 36 hours of arrival to the emergency department. Nasopharyngeal and bronchoalveolar washings were negative for influenza A and B by rapid test and DFA. Tests for RSV, adenovirus, parainfluenza virus, and *Legionella* were negative. Subsequently, 2009 H1N1 influenza A virus was detected in the nasopharyngeal wash specimen by real-time RT-PCR. Bacterial culture of respiratory tract specimens showed moderate growth of *Streptococcus pyogenes*.

#### Case 6d Discussion: 2009 H1N1 influenza

#### Epidemiology and Clinical Presentation

Since the first identification of a novel influenza virus causing human infections in the spring of 2009, the 2009 H1N1 influenza A virus rapidly spread across the world. On June 11, 2009, less than three months after the first cases were recognized, the World Health Organization (WHO) increased the pandemic alert level to 6, indicating that a global pandemic was underway. The pandemic was classified by WHO as “moderate” in its severity, based on the findings that most people recovered from infection without the need for hospitalization or medical care, levels of severe illness appeared similar to levels seen during local seasonal influenza periods, and hospitals and healthcare systems were generally able to cope with the numbers of people seeking care.

The Centers for Disease Control and Prevention (CDC) estimate that between April and November 2009 there were 34–67 million cases of 2009 H1N1 infection in the United States, with approximately 213,000 hospitalizations and 9,820 deaths (http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm). Unlike seasonal influenza, the great majority of these cases, hospitalizations, and deaths have occurred among persons younger than 65 years of age. Factors that have been associated with severe and/or complicated

disease include age less than 2 years or greater than 65 years, pregnancy, and the presence of underlying medical conditions that have previously been associated with a higher risk of influenza complications (e.g., asthma, diabetes, immunosuppression).

The clinical manifestations of 2009 H1N1 influenza A infection are largely indistinguishable from those of seasonal influenza, with most patients experiencing fever and cough, and many experiencing other typical influenza symptoms such as malaise, myalgias, and headache. GI symptoms such as nausea, vomiting, and diarrhea have been reported in approximately 25%–30% of cases, more common than has typically been reported with seasonal influenza infection.

Causes of mortality associated with 2009 H1N1 influenza include viral pneumonia, acute respiratory distress syndrome, multiorgan system failure, and bacterial superinfection. Concurrent bacterial pulmonary infection has been identified in 29%–55% of fatal cases.[1,2] identified bacterial pathogens have included *S. pneumoniae*, *S. aureus* (including MRSA), Group A *Streptococcus,* and *Streptococcus mitis*.

## Diagnosis

In many cases, specific testing for influenza is not necessary, and the diagnosis can be made clinically based on a patient's symptoms and signs. Studies performed in the setting of seasonal influenza have shown that the accuracy of a clinical diagnosis may equal or surpass that of some laboratory tests in patients with typical influenza-like illness, when influenza is known to be circulating in the community.

A number of laboratory tests are available for the detection of influenza viruses in respiratory tract specimens. These tests include rapid tests, direct fluorescent antigen (DFA) tests, viral culture, and polymerase chain reaction (PCR). Most tests can distinguish influenza A viruses from influenza B viruses; however, only PCR-based testing is currently able to distinguish among influenza A viruses. In terms of the performance characteristics of the various testing methods, studies during the first wave of the pandemic demonstrated that the sensitivity and negative predictive values of rapid tests and DFA tests for the detection of the 2009 H1N1 virus were relatively low.[3,4] Based on these findings, a negative result should not be considered to rule out a diagnosis of 2009 H1N1 influenza infection. Viral culture and PCR-based testing have been demonstrated to have much greater sensitivity and negative predictive values.

## Pathology

H1N1 influenza virus, similar to all other influenza viruses, targets the ciliated epithelium of the tracheobronchial tree, producing a spectrum of changes depending on the stage of the disease and the presence or absence of superimposed bacterial pneumonia. Two recent reports from the United States and Brazil describe in detail the pathologic changes of fatal novel H1N1 influenza infection.[2,5] Macroscopically, the lungs are always heavy, edematous with areas of consolidation and variable degrees of hemorrhage. At the microscopic level, the pathologic changes include necrotizing tracheobronchitis and bronchiolitis, diffuse alveolar damage (DAD) ranging from focal to diffuse (Figure **6d.2**), as well as variable pulmonary edema and alveolar hemorrhage. DAD is usually of the exudative type with alveolar and interstitial edema, fibrinous exudate, reactive pneumocytes, and hyaline membranes. Pulmonary thrombi with evidence of infarction are sometimes seen as part of the spectrum of DAD (Figure **6d.3**).

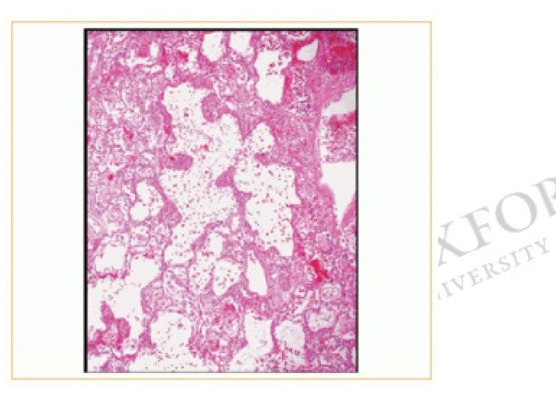




Figure 6d.2
Lung parenchyma from post mortem examination showing necrotizing tracheobronchitis and bronchiolitis, diffuse alveolar damage ranging from focal to diffuse as well as variable pulmonary edema and alveolar hemorrhage.

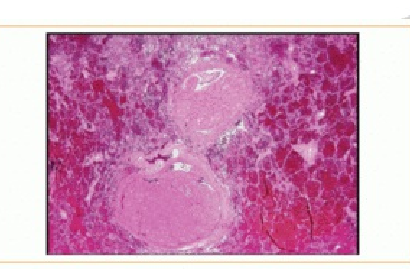




Figure 6d.3
Lung parenchyma from post mortem examination showing pulmonary thrombi with evidence of infarction as part of the spectrum of diffuse alveolar damage.

The large cartilaginous airways typically exhibit epithelial necrosis and squamous metaplasia, while smaller airways show necrotizing bronchiolitis with extensive necrosis of the bronchiolar wall and dense neutrophilic infiltrates within the bronchiolar lumen. Epithelial damage to the airway provides a portal for bacteria such as streptococci and staphylococci, which can lead to acute bronchopneumonia ranging from focal to diffuse and necrotizing. Since the viruses produce no characteristic cellular inclusions, identification requires antigen detection by immunohistochemistry, or immunofluorescence with positivity predominantly in the epithelium of the tracheobronchial tree and submucosal glands and, to a lesser extent, in the bronchiolar epithelium, alveolar epithelial cells, and macrophages.

## Treatment

Most patients with influenza infection, including 2009 H1N1 influenza, recover from the illness without specific treatment. Symptomatic treatment typically consists of fever suppressants, analgesics, cough suppressants, and adequate hydration. Antiviral therapy is recommended for persons with confirmed or suspected influenza who have underlying conditions that place them at increased risk of complicated or severe disease, and for those who require hospitalization. In these patients, empiric antibacterial

therapy should also be initiated if there is clinical suspicion of bacterial coinfection. Decisions to initiate antiviral treatment of other persons should be made on a case by case basis. In these lower-risk persons, treatment is most likely to provide benefit (i.e., reduction in duration of symptoms) if provided within 48 hours of the onset of symptoms.

A neuraminidase inhibitor, oseltamivir or zanamivir, is currently considered to be the treatment of choice for 2009 H1N1 influenza A viruses because these viruses are resistant to the adamantanes (i.e., amantadine and rimantadine). For hospitalized patients who are failing treatment with oral or inhaled neuraminidase inhibitor therapy, or in whom oral or inhaled therapy is not possible, a treatment alternative is the intravenously administered neuraminidase inhibitor, peramivir. Although not FDA approved, the FDA has issued an Emergency Use Authorization for this agent. It should be noted, however, that the mutation (H275Y) that has been associated with oseltamivir resistance also results in resistance to peramivir. An intravenous formulation of zanamivir is currently available from the manufacturer for compassionate use. Isolates with the H275Y mutation retain susceptibility to zanamivir.[6]

## Prevention

Several general infection control measures may be helpful in preventing transmission of influenza. These measures include hand hygiene, respiratory etiquette (e.g., using tissues, covering one's mouth and nose when coughing and sneezing), avoiding contact with sick persons, and staying home when ill. Within healthcare facilities, the risk of transmission can be reduced through early recognition of possible cases of influenza, provision of surgical masks and tissues to patients with influenza-like illness, physical and spatial separation of symptomatic patients from others, and implementation of appropriate transmission-based precautions.

Vaccination is considered to be the one of the most important components of an influenza prevention program. In response to the 2009 pandemic, which occurred after production of the 2009–2010 trivalent seasonal influenza vaccine had already begun, a monovalent 2009 H1N1 influenza A vaccine was developed. In clinical studies, the vaccine has been shown to be highly immunogenic in children and adults.[7,8]

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## Three Men with Severe Pneumonia after Entering a Mine

**Chapter:** Three Men with Severe Pneumonia after Entering a Mine
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0030

### Case Presentation

A 65-year-old man from Germany entered a mine in Mexico that had been out of operation for nearly thirty years. He and his coworkers from Mexico and Sweden noted the presence of numerous bats and bat droppings when the doors were opened. Two weeks later, he and his colleagues were in their respective countries when they each developed decreased appetite, dry cough, dyspnea, drenching sweats, and fevers to 40° C.

The German patient was evaluated by a physician in Berlin and hospitalized with respiratory distress. On physical examination he was tachypneic (25 breaths per minute), febrile to 38.5° C, and hypoxic (oxy-gen saturation, 90% on ambient air). Pulmonary auscultation was significant for decreased breath sounds in bilateral bases. His laboratory examinations were mainly notable for mild elevation of the hepatic enzymes ALT 191, AST 132, LDH 360, and GGT 98. Thoracic imaging revealed bilateral nodular infiltrates, dense consolidations, and pleural effusions (Figures **6e.1**, **6e.2a**, and **6e.2b**). A transthoracic echocardiogram revealed trace pulmonary hypertension, and abdominal ultrasound revealed the presence of mild hepatic enlargement.

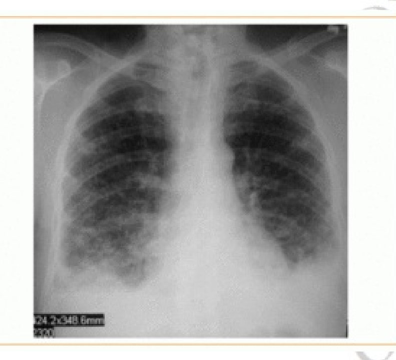


Figure 6e.1
Chest radiograph, posterior-anterior view with bilateral pleural effusions and diffuse bilateral nodular infiltrates.

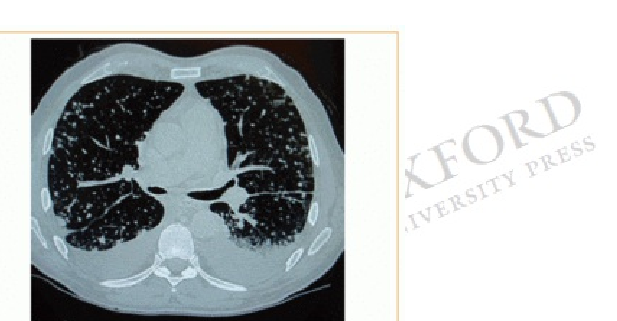


Figure 6e.2a
CT scan lungs, axial view with bilateral pleural effusion and diffuse bilateral miliary nodules.






Figure 6e.2b
CT scan lungs, axial view after therapy with resolution of bilateral pleural effusion and persistence of diffuse bilateral miliary nodules.

The patient underwent bronchoscopy with transbronchial biopsy, but no organisms were seen on Gram stain, acid-fast stain, or Gomori methenamine silver stains. He was presumptively treated for pulmonary histoplasmosis with liposomal amphotericin B followed by itraconazole. Four weeks later (upon evaluation in the United States) the patient's urine *Histoplasma* antigen was moderately positive (5.23 ng/ml) and the CT scan revealed diffuse miliary nodules (6e-3). The urine *Histoplasma* antigen eventually declined to undetectable levels with completion of antifungal treatment. The two patients in Mexico and Sweden were also confirmed to have pulmonary histoplasmosis, and responded well to similar therapies in their respective countries.

**Case 6e Discussion: *Histoplasma capsulatum***

## Diagnosis and Clinical Features

*Histoplasma capsulatum* is a dimorphic fungus found in all areas of the world where warm moist soil is present and promotes the growth of the mycelial phase of the organism. In the United States, the areas of highest endemicity are in the Midwest states, along the banks of the Ohio River. The organism is commonly found throughout Central and South America, and it was originally described in Panama by the pathologist Samuel Darling, who believed it to be a protozoan parasite similar to *Leishmania.* The organism is associated with cave and mine exploration because of the presence in bat guano that enhances fungal sporulation.[1]

The clinical manifestations of histoplasmosis vary greatly depending on the immune status of the host. Initial inhalation of the infectious particles can lead to severe disease in immunocompetent hosts if the inoculum is large enough, but many individuals are asymptomatically infected. Patients may present with nonproductive cough, dyspnea, fevers, and sweats. Progressive disseminated disease is also characterized by pancytopenia, hepatic and splenic enlargement, and profound weight loss. Liver enzyme elevation with markedly elevated lactate dehydrogenase levels may be important diagnostic clues in patients with AIDS and disseminated histoplasmosis. Unrecognized cases may progress to respiratory failure and septic shock.[2]

In immunocompetent hosts, chronic inflammatory conditions such as mediastinal fibrosis may occur. This complication is characterized by chronic scarring of the mediastinal lymph nodes that are in close proximity to the great vessels and airways of the mediastinum. It is poorly responsive to antifungal therapy or steroids, and in a minority of cases can be fatal. Mechanical stenting of the great vessels is a therapeutic option for this condition.[1]

Disseminated histoplasmosis is most frequently seen in immuno-compromised patients, such as those with advanced AIDS, organ transplant recipients, and patients with inflammatory conditions treated with other immunosuppressive therapies. Recent cases of disseminated histoplasmosis in patients taking biologic agents such as infliximab and etanercept highlight the importance of immune control in preventing reactivation illness.[3] infliximab, an antitumor necrosis factor monoclonal antibody, appears to impart a greater risk of reactivation of granulomatous disease than etanercept, a soluble tumor necrosis factor receptor, but both can pose a risk to patients with previous exposure to *Histoplasma capsulatum*.[3] Figure **6e.3** is a biopsy of a large pulmonary nodule that developed in a patient who was taking etanercept for severe rheumatoid arthritis. She had previously lived in Tennessee 4 years prior to moving to New York. AIDS patients with disseminated histoplasmosis may present with severe sepsis, acute respiratory distress syndrome, and signs of adrenal insufficiency.

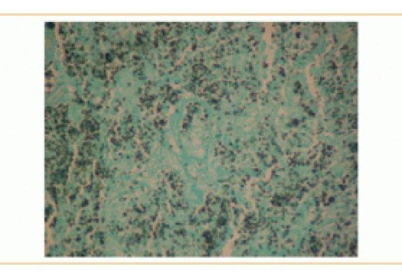





Figure 6e.3
Lymph node biopsy, Gomori methenamine silver stain. Innumerable small (2–4 microns) budding yeast cells consistent with *Histoplasma capsulatum*.

The diagnosis of histoplasmosis can be established by visualization of the organism in biopsied tissue (Figure **6e.3**), bronchoalveolar lavage fluid (Figure **6e.4**), or the peripheral blood smear (Figure **6e.5**) of severely immunosuppressed patients. The organism can also be recovered in cultures where the mycelial phase of the organism can be appreciated (Figures **6e.6** and **6e.7**). The *Histoplasma* urine antigen test is rapid and highly accurate in the setting of immunosuppressed patients with disseminated disease.[2] For patients with no underlying immune deficiency and low inoculums, the urine antigen test may be falsely negative, though in some settings this diagnostic problem may be overcome using concentration methods.[4] The usefulness of serology is limited in the diagnosis of acute histoplasmosis, particularly in areas in which asymptomatic exposure is common.[2]

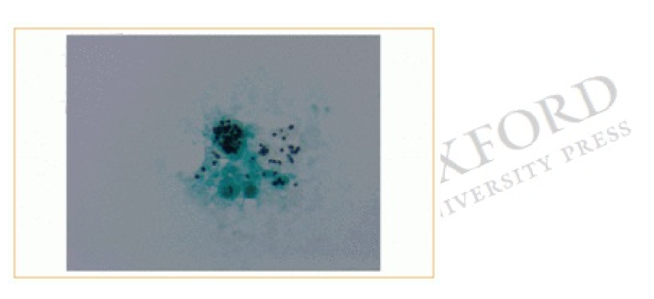




Figure 6e.4
Bronchoalveolar lavage specimen, Gomori methenamine silver stain with budding yeast cells of *Histoplasma capsulatum*.

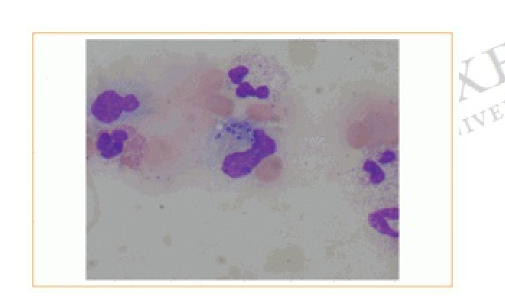


Figure 6e.5
Peripheral blood smear (Wright-Giemsa stain) with intracellular budding yeast in a patient with disseminated histoplasmosis.

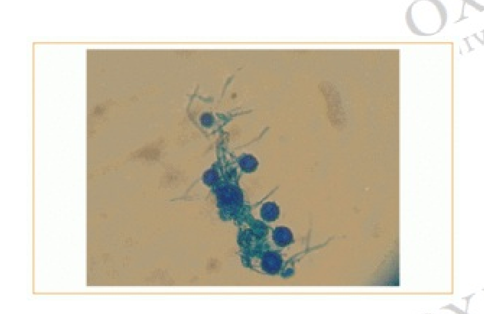




Figure 6e.6
Lactophenol blue stain of culture of *Histoplasma capsulatum* showing the tuberculate macroconidia of the mycelial phase when grown at 24°C.





Figure 6e.7
Macroscopic appearance of mycelial colonies of *Histoplasma capsulatum* when grown at 24°C on Sabaroud's dextrose agar.

The radiologic appearance of the CT scan in this case with diffuse nodular infiltrates was representative of the typical appearance of pulmonary histoplasmosis on radiographic imaging. Many of the radiologic findings of pulmonary histoplasmosis (hilar lymph node enlargement, miliary infiltrates, pleural or pericardial effusions) mimic tuberculosis, and the clinical symptoms of fevers, night sweats, weight loss, and dyspnea also over-lap. The histologic appearance of granulomas may also prompt suspicions of tuberculosis, but staining with Gomori methenamine silver (GMS) stain reveals the 2–4-micron ovoid, budding yeast cells demonstrated in Figure **6e.4**.[2]

Laboratory studies are often helpful in the diagnosis of disseminated histoplasmosis in patients with AIDS or other forms of immunosuppression. Pancytopenia and elevated liver enzymes are often hallmarks of the disease. Extremely elevated lactate dehydrogenase (LDH) levels are also a differentiating laboratory finding. *Histoplasma* serology is of little practical use in separating prior exposure from acute infection in patients who live in endemic areas. The urine *Histoplasma* antigen has proven itself to be the most reliable diagnostic test in patients with disseminated forms of the disease. Immunocompetent patients who have mild, self-limited histoplasmosis may have false negative urine antigen testing.[1]

## Management

Many patients with mild forms of pulmonary histoplasmosis will have a self-limited illness that does not require treatment. Immunocom-promised patients with disseminated disease and immunocompetent patients with moderate to severe pulmonary disease may be managed with antifungals, such as amphotericin and itraconazole. Lipid formulations of amphotericin have shown superiority over conventional amphotericin deoxycholate in adults with histoplasmosis.[1] induction treatment regimens with intravenous amphotericin for 7–14 days are followed by maintenance treatment with oral itraconazole for several months in immunosuppressed patients. Echinocandins do not demonstrate in vitro activity against *Histoplasma*, and therefore are not recommended. Newer triazole antifungals have demonstrated in vitro efficacy, and are especially useful for patients who do not tolerate itraconazole. Echinocandins do not demonstrate in vitro activity against *Histoplasma*, and therefore are not recommended.[1]

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## A 73-Year-Old Man with Nosocomial Pneumonia

**Chapter:** A 73-Year-Old Man with Nosocomial Pneumonia
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 73-year-old man with a history of benign prostatic hypertrophy, hypertension, and chronic obstructive pulmonary disease was admitted for surgical management of a 5.7 cm thoracoabdominal aortic aneurysm (Figure **7a.1**). He underwent aneurysm resection and graft replacement of the aorta from the midthoracic to the infrarenal portion.






Figure 7a.1
CT reconstruction of thoracoabdominal aortic aneurysm.

The patient's perioperative course was complicated by difficult ventilation and reintubation for hypoxia and atrial fibrillation on the first postoperative day. Over the next several days, he developed agitation, fever (38.5 °C), hypotension requiring vasopressors, and peripheral cyanosis in bilateral lower extremities. His laboratory studies showed progressively worsening leukocytosis (peak 34.5 $\times 10^3$ WBC/ul, 40% bands), thrombocytopenia ($34\times10^3$ platelets/ul), acute kidney injury (creatinine 2.8 mg/dl), and hepatic failure (AST 2847 U/L, ALT 712 U/L, bilirubin 8.8 mg/dl). Chest imaging showed dense bilateral consolidations that worsened over the course of a week (Figures **7a.2** and **7a.3**), and both blood and sputum cultures grew *Pseudomonas aeruginosa* susceptible to ciprofloxacin and imipenem (Figure **7a.4**).






Figure 7a.2
Chest radiograph, anterior-posterior view showing bilateral pulmonary consolidations.









Figure 7a.3
CT lungs, axial view showing dense bilateral consolidations.

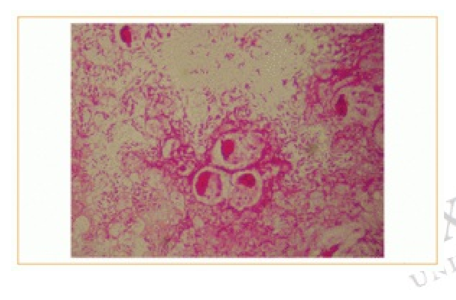


Figure 7a.4
Endotracheal secretions, Gram stain showing innumerable Gram-negative bacilli and polymorphonuclear cells.

A rising serum lactate (7.7 mmol/L) caused concern for concomitant intestinal ischemia; however, an exploratory laparotomy showed no signs of ischemia or aortic graft defect. Despite broad spectrum antibiotics including imipenem, the patient died on the tenth postoperative day.

**Pathology**

At autopsy, the lungs were markedly edematous and consolidated, with bilateral necrotizing abscesses and areas of parenchymal hemorrhage (Figure **7a.5**). The pulmonary parenchyma exhibited severe emphysematous changes with subpleural blebs. Histologically, the alveolar spaces were filled with acute inflammatory infiltrates, predominantly neutrophils, with fibrin deposition and coagulative necrosis (Figure **7a.6**). Foci of aspirated vegetable matter and large bacterial colonies were observed. Gram stain revealed Gram-negative rods, and postmortem lung tissue cultures grew *Pseudomonas aeruginosa*.






Figure 7a.5
Lungs on postmortem examination were markedly edematous and consolidated with bilateral necrotizing abscesses and areas of parenchymal hemorrhage. The pulmonary parenchyma exhibited severe emphysematous changes with subpleural blebs.

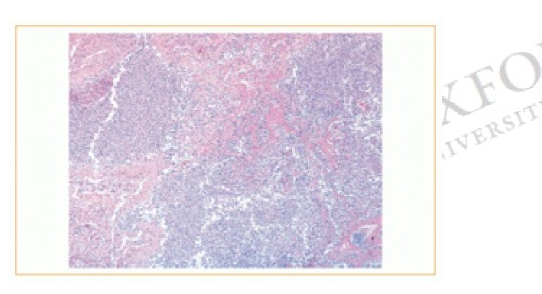





Figure 7a.6
Histologic section of lungs on postmortem examination showing alveolar spaces filled with acute inflammatory infiltrates, predominantly neutrophils, with fibrin deposition and coagulative necrosis.

**Case 7a Discussion: *Pseudomonas aeruginosa***

## Clinical Presentation and Diagnosis

Pneumonia is the second most common healthcare-associated infection, and is a significant contributor to healthcare-associated morbidity and mortality.[1] Hospital acquired pneumonia (HAP) should be suspected in a hospitalized patient with a radiographic infiltrate that is new or progressive, along with clinical findings suggesting infection, including new onset of fever, purulent sputum, leukocytosis, or worsening oxygenation. Ventilator-associated pneumonia (VAP), a subset of HAP, is an important complication in patients requiring mechanical ventilation. The diagnosis of suspected HAP may be supported by chest radiography with posterior-anterior and lateral views, two sets of blood cultures, sputum Gram stain and culture, complete blood count and chemistry, and urine *Legionella* antigen testing. Urine pneumococcal antigen testing may also be useful in guiding antimicrobial therapy; however, its role is controversial.[2]

Hospital acquired pneumonia can be caused by a diverse range of pathogens; bacteria are most common, and can include organisms traditionally associated with community-acquired pneumonia (CAP) such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. An increasing percentage of cases, however, are due to Gram-negative organisms, as well as methicillin-resistant *Staphylococcus aureus* (MRSA).[1,3] *Pseudomonas aeruginosa* has been implicated in up to 18% of HAP cases, and is seen much more frequently in nosocomial pulmonary infections than in those acquired in the community (Table 7a.1).[2]

Table 7a.1 Important Pathogens in Nosocomial Pneumonia by Prevalence

| |
|---|
| Methicillin-resistant *Staphylococcus aureus* |
| *Streptococcus pneumoniae* |
| *Pseudomonas aeruginosa* |
| Methicillin-sensitive *Staphylococcus Aureus* |
| *Haemophilus* species |
| Other Gram-negative rods |
| Enterobacteriaceae |
| *Klebsiella* Species |
| *Escherichia coli* |
| *Legionella* Species |

*Source*: Micek et al. Healthcare-associated pneumonia and community-acquired pneumonia: a single-center experience. *Antimicrob Agents Chemother.* 2007; 51:3568–3573.

*Pseudomonas aeruginosa* is the most common multidrug-resistant (MDR) Gram-negative pathogen causing pneumonia in hospitalized patients.[4] It elaborates several virulence factors that are important in its pathogenesis, including pili, proteases, lipopolysaccharide, exotoxins, and biofilms. Patients with structural lung disease or extensive smoking history are at greater risk of pseudomonal pneumonia because of ineffective clearance of the organism. *Pseudomonas aeruginosa* thrives in hospital water sources, such as mechanical ventilator tubing. Microbiologic confirmation should be pursued in patients with enhanced risk of *Pseudomonas aeruginosa* pneumonia to aid in determination of appropriate antimicrobial therapy.[5]

## Management

Antibiotics with antipseudomonal activity include the aminoglycosides, ticarcillin, piperacillin, ceftazidime, cefepime, aztreonam, the carbapenems (except for ertapenem), ciprofloxacin and levofloxacin.[5] Higher-dose therapy is suggested in cases of suspected pseudomonal pneumonia due to intrinsic resistance in this organism. The optimal antipseudomonal antibiotic choice is difficult because of a dearth of experimental evidence, but prospective data has suggested that isolates may become resistant to imipenem faster than to fluoroquinolones or cephalosporins. Among the fluoroquinolone antibiotics, ciprofloxacin is the most potent antipseudomonal agent.[4,5] The use of combination therapy with two classes of antibiotics for *Pseudomonas* infection is controversial, but the use of aminoglycosides as a single agent has been associated with a higher failure rate.[5] Prospective studies have suggested that empiric dual therapy may be associated with greater rates of microbiologic cure and lower incidences of antimicrobial resistance, but limited data exists to support a mortality benefit with this strategy.[5] Patients with known MDR pseudomonas colonization, or with previous exposure to antipseudomonal antibiotics, may benefit the most from dual therapy.[5]

Because of enhanced risk of *Pseudomonas* and other resistant Gram-negative pathogens in hospital acquired pneumonias, empiric antibiotic regimens should take into consideration both local and institution-specific antimicrobial susceptibility profiles, as well as the patient's underlying immune status. Empiric therapy for healthcare-associated pneumonia should include a b-lactam antibiotic with antipseudomonal activity, and vancomycin or linezolid for empiric MRSA coverage if local or institutional MRSA rates are high.[4] Response to therapy should be monitored, and results of initial diagnostic testing, including culture data and bacterial antigens, can be used to streamline the initial antimicrobial regimen. Patients that do not improve within 48–72 hours of initial antimicrobial therapy should be considered for additional diagnostic testing including bronchoscopy with bronchoalveolar lavage, and evaluation for non-bacterial pathogens or alternate diagnoses.[4]

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## A 72-Year-Old Woman with Persistent Cough and Neutropenia

**Chapter:** A 72-Year-Old Woman with Persistent Cough and Neutropenia
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 72-year-old woman from Russia with a history of breast cancer and non-Hodgkin's lymphoma was subsequently diagnosed with acute myelogenous leukemia. She was treated with a chemotherapy regimen that included decitabine and azacitidine, and several days later developed febrile neutropenia. She was empirically treated with vancomycin and cefepime, and discharged with levofloxacin after resolution of fever. Three days later she was readmitted with recurrent fever, chills, headache, and worsening cough with clear sputum.

On physical examination, her maximum temperature was 38.1° C, and she was noted to have rigors in the emergency department. She had slightly decreased breath sounds and a few wheezes and rales in both lung bases, but the remainder of her physical examination was unrevealing. Her laboratory studies were significant for leukopenia (WBC 0.7 × $10^3$ WBC/µl, 16% polymorphonuclear cells, 68% lymphocytes, 8% blasts), anemia (hemoglobin 9.9 gm/dl), thrombocytopenia (platelets 6 × $10^3$ WBC/µl) and elevated lactate dehydrogenase (445 U/L).

Initial chest radiography revealed slightly increased interstitial markings, and a high-resolution CT scan of the lungs three days later showed patchy alveolar consolidations with surrounding ground glass opacities (Figure **7b.1** and **7b.2**). She was empirically treated with vancomycin and cefepime, but continued to have cough and low grade fevers. A sputum sample for respiratory viruses was collected, and the direct fluorescence antibody for respiratory syncytial virus was positive (Figure **7b.3**). Her fever and cough abated with supportive care, and she was discharged with oral levofloxacin as a prophylactic agent until her neutropenia resolved.

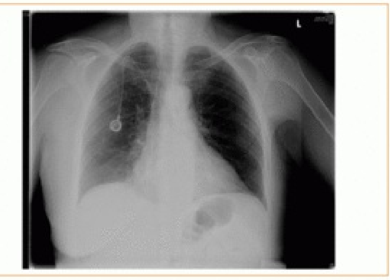





Figure 7b.1
Chest radiograph, posterior-anterior view with mildly increased interstitial markings.






Figure 7b.2

High resolution CT scan of the lungs, axial view showing patchy alveolar consolidations with surrounding ground glass opacities.

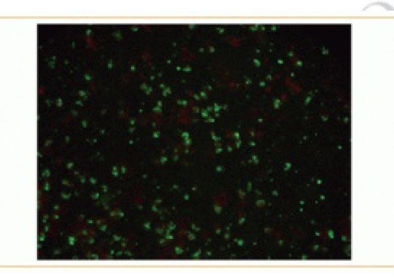




Figure 7b.3
Direct fluorescence antibody test showing green fluorescence where RSV antigens are present.

**Case 7b Discussion: Respiratory Syncytial Virus**

## Clinical Presentation and Diagnosis

Respiratory syncytial virus (RSV) is a common cause of serious illness in children and immunocompromised adults, particularly among hematopoietic stem cell transplant (HSCT) and lung transplant recipients. The virus is readily transmitted by contact with infected respiratory secretions, and can cause disease of the upper and lower respiratory tract. Higher rates of RSV are seen during winter months in temperate climates, and the virus is responsible for hundreds of thousands of hospitalizations of children and adults each year. By the first year of life, most children have been exposed to RSV; however, immunity is not protective because of seasonal antigenic variation.[1]

Disease in both children and adults may begin as upper airway disease and progress to lower airway disease, including bronchiolitis and pneumonia. Initially, patients may present with nasal congestion, cough, and fever, but then progress to dyspnea, tachypnea, and respiratory failure. Physical examination may be notable for wheezing and crackles when bronchiolitis and pneumonia are present. Among HSCT recipients, 40%–50 % of those presenting with upper respiratory tract disease will progress to lower respiratory tract disease, and the mortality of HSCT recipients with lower tract RSV disease approaches 80%.[1,2] Since RSV is the most common respiratory virus to cause infection in this population, efforts at early diagnosis, treatment, and prevention are crucial.

Radiographic findings can range from diffuse ground-glass opacities to focal alveolar airspace consolidations. Children and adults with RSV disease may also present with hyperinflation of the lungs as a result of air trapping.[1] Confirmation of RSV pneumonia can be achieved with viral culture, PCR, or direct fluorescence antibody testing on samples from bronchial washings, sputum, or nasal washings. Rapid antigen tests are also available, with sensitivity ranging from 50%–90% and specificity ranging from 73%–100%.[1]

## Management

No definitive guidelines have been published regarding the optimal management of RSV in the adult immunocompromised population, and large controlled trials are lacking. Aerosolized ribavirin has been used to treat HSCT recipients with both upper airway and lower airway RSV disease.[3] A major limitation of this strategy is that ribavirin is teratogenic and, therefore, potentially a risk to healthcare workers caring for patients treated with ribavirin.[3,4] In a multicenter study in which fourteen patients with upper respiratory tract infection with RSV were randomized to receive either aerosolized ribavirin or supportive care, no significant difference in progression to lower respiratory tract disease was observed. Although a trend toward lower levels of viral load in nasal washings was observed, the difference was not statistically significant.[4]

Palivizumab is an RSV-specific monoclonal antibody that has been shown in murine models to significantly reduce the RSV viral load.[2] In humans, it has been studied mainly in children with RSV infection; however, small trials in adults have also been conducted.[2] In a retrospective analysis of 40 allogeneic stem cell transplant recipients with symptomatic RSV infection, 19 received palivizumab, while a control group was treated mainly with supportive care and, in some cases, intravenous ribavirin. In comparing the groups, no significant differences were seen in progression to lower respiratory tract disease or in overall survival.[2]

RSV is readily transmitted by contact with infectious secretions that contaminate surfaces, and self-inoculation via mucous membranes. Patients with RSV disease should therefore be placed on contact isolation during their hospitalization; transmission via airborne particles appears to play a less important role and respiratory isolation is not necessary.[1] The use of prophylactic palivizumab in high-risk infants or adult HSCT recipients remains controversial because of limited supportive data and high cost.

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## A 56-Year-Old Woman with Pulmonary Nodules

**Chapter:** A 56-Year-Old Woman with Pulmonary Nodules
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 56-year-old woman with a history of asthma and refractory non-Hodgkin's lymphoma underwent allogeneic bone marrow transplantation from her HLA-identical sister. Her course was complicated by pulmonary embolism and several episodes of graft versus host disease of the skin, treated with increased immunosuppression. One year after her transplant she had engrafted and was in remission. Her medications included mycophenolate mofetil, prednisone, albuterol, dalteparin, valacyclovir, trimethoprim-sulfamethoxazole, and fluconazole. She presented with dyspnea, chest tightness and wheezing, and was admitted with a presumed asthma exacerbation. She also noted fever, cough, and pleuritic chest pain.

On physical examination she was in no acute distress, but she was febrile (38.1°C), hypoxic (oxygen saturation 92% on ambient air), and her pulmonary examination was notable for wheezing. Her initial laboratory values were significant for leukocytosis (15.7 WBC × $10^3$ WBC per µl, 74% neutrophils) and mildly elevated lactate dehydrogenase (267 U/L). A CT scan of the lungs identified a new cluster of nodules and associated bronchiectasis in the right lower lobe (Figure **7c.1**) and the patient underwent flexible bronchoscopy and video-assisted thoracoscopy with lung biopsy.

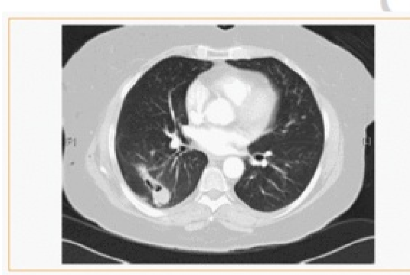





Figure 7c.1
CT scan of the lungs, axial view showing a cluster of nodules and associated bronchiectasis in the right lower lobe.

Histopathologic examination of the lung tissue revealed thin, septated hyphae with acute-angle branching (Figures **7c.2**, **7c.3**, and **7c.4**). While the fungal cultures of the lung biopsy were sterile, the cultures from the bronchial washings grew *Aspergillus fumigatus* (Figures **7c.5** and **7c.6**). The patient was initially treated with intravenous liposomal amphotericin, and eventually discharged with oral voriconazole.

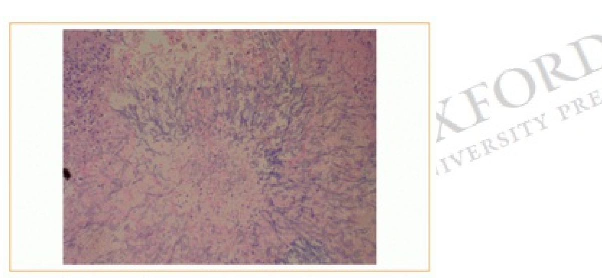





Figure 7c.2
Lung biopsy, hematoxylin and eosin stain showing angioinvasive fungal hyphae with septations and and acute-angle branching.

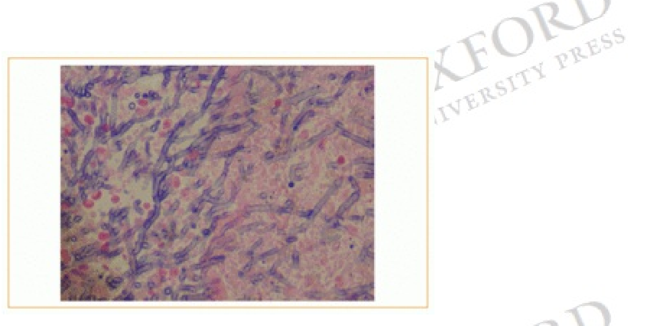




Figure 7c.3
Lung biopsy, hematoxylin and eosin stain at higher magnification showing thin septated hyphae with acute-angle branching.

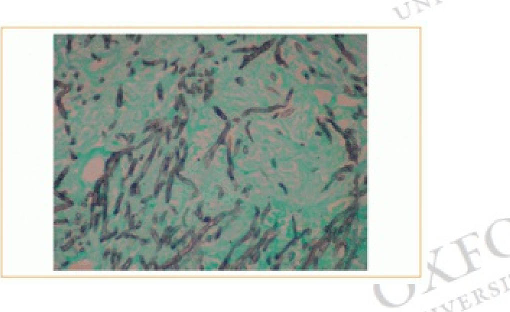


Figure 7c.4
Lung biopsy, Gomori methenamine silver stain showing angioinvasive fungal hyphae with thin septated hyphae with acute-angle branching.

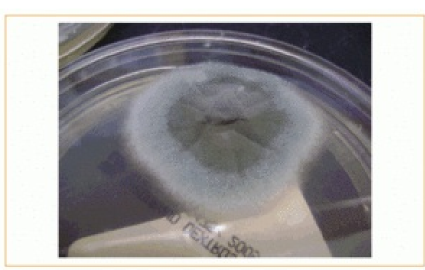




Figure 7c.5
Culture of bronchial washing with mycelial colony *Aspergillus fumigatus*.





Figure 7c.6
Culture of bronchial washing, lactophenol blue stain showing microscopic appearance of *Aspergillus fumigatus* with conidiophore (fruiting head) and columnar conidia.

**Case 7c Discussion: *Aspergillus fumigatus***

## Clinical Presentation and Diagnosis

*Aspergillus* species are a group of ubiquitous hyaline molds which produce a wide range of clinical disease. Allergic bronchopulmonary aspergillosis (ABPA) is most commonly seen in chronic asthmatics who develop a hypersensitivity reaction to *Aspergillus* resulting in increased symptoms, peripheral blood eosinophilia, and pulmonary infiltrates. Pathologically, ABPA is characterized by mucoid impaction of the bronchi with “allergic mucin” containing eosinophils and fungal hyphae; the bronchi and surrounding lung may show bronchiectasis, asthma-like changes, or eosinophilic pneumonia. In some cases, histologic findings of bronchocentric granulomatosis may be seen. Aspergilloma results from *Aspergillus* colonizing a preexisting cavity in the lung. The cavity may be secondary to a variety of causes, including prior tuberculosis or other granulomatous infection, bronchiectasis, or resolved abscess. These are generally benign forms of aspergillosis in comparison to the consequences of invasive aspergillosis in immunocompromised hosts.

Invasive pulmonary aspergillosis is one of the major life-threatening complications in immunocompromised patients, such as hematopoietic or solid organ transplant recipients, and neutropenic patients following cancer chemotherapy.[1,2] The spores of the organism are inhaled routinely from the environment, and thus the initial site of invasive disease

is typically the lungs or sinuses. In immunocompromised hosts, the organism can then disseminate via the bloodstream to multiple sites including the central nervous system, where the mortality of invasive disease is greatest.[1] The degree and duration of neutropenia directly correlates with the risk of invasive disease over time. Increased immunosuppression to treat graft versus host disease is also a major risk factor. Mortality from invasive disease remains high, even with early recognition and early therapy, and favorable outcomes in patients with hematopoietic stem cell transplants range from only 20%–40%.[1,3]

Patients with invasive pulmonary aspergillosis may present with undifferentiated fever, but cough, dyspnea, and pleuritic chest pain may also be part of the presenting syndrome. Radiographic findings on CT scans of the lungs vary from diffuse pulmonary infiltrates and ground-glass opacities to cavitary nodules with surrounding areas of infarction. The presence of a halo sign (a pulmonary nodule with surrounding ground-glass attenuation) or air-crescent sign (crescent-shaped or circumferential area of radiolucency within a cavity or parenchymal consolidation) suggests the angioinvasive nature of this mold in immunocompromised hosts.[1]

Diagnosis of pulmonary invasive pulmonary aspergillosis remains a clinical challenge because of several factors. Although sputum or bronchoalveolar lavage cultures may be successful in isolating the organism, they lack sensitivity and a false positive result may represent airway colonization. Radiographic studies may be helpful but lack of specificity does not allow for differentiation from other invasive mold infections (agents of mucormycosis) or from noninfectious causes of nodules such as malignancy. Lung biopsy (via transbronchial approach, or via video-assisted thoracoscopy) remains the gold standard for a definitive diagnosis of proven invasive aspergillosis; however, the risks of these invasive procedures in the setting of profound thrombocytopenia (often the case in hematopoietic stem cell transplant recipients) often limit their feasibility.[1]

The morphologic appearance of the hyphae in histologic specimens may help distinguish *Aspergillus* from other invasive molds such as the agents of mucormycosis. The hyphae of *Aspergillus* are typically thinner, with septations and acute angle branching, while those of the agents of mucormycosis are broad, ribbon-like, lacking septations, and branching at right angles. Areas of invasive aspergillosis are characterized by hemorrhage, infarction, and necrosis, given the predilection for the organisms to invade blood vessels. Calcium oxalate crystals may be seen in association with the organisms, especially with *Apergillus niger*. Invasive aspergillosis and mucormycosis are both characterized by hemorrhage, infarction, and necrosis. The organism may be visible on hematoxylin and eosin staining, but Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains serve to highlight the presence of hyphae within the tissues.[1]

While the organism can be recovered on standard media from tissue biopsies, blood cultures are rarely positive even in cases of disseminated disease. *Aspergillus fumigatus* is the species most frequently isolated in patients with invasive pulmonary aspergillosis, but other species such as *A. flavus*, *A. niger*, and *A. terreus* are also detected. On standard culture media the organism grows within 48–72 hours and produces pigmented, feathery colonies. Microscopic examination of hyphae stained with lactophenol blue reveal the typical sporulating head with small round conidia. The genus derives its name from its similarity to the hollow tube used in Catholic mass to spread holy water, the *aspergillum*. Antimicrobial susceptibility testing of *Aspergillus* species is now available, though clinical correlation is still lacking. Certain species such as *A. terreus* are usually resistant to amphotericin B, and resistance testing is advisable.[1]

The role of non-culture-based assays such as galactomannan detection has emerged in the diagnosis of invasive aspergillosis. Galactomannan is a polysaccharide cell wall component of *Aspergillus* that is released as the organism multiplies. The use of enzyme immunoassay for the detection of galactomannan may allow for early detection of invasive aspergillosis with sensitivities ranging from 57%–87.5% in hematopoietic stem cell transplant recipients have been reported. The specificity of the assay has been reported to be 92%–100% in this group, but several conditions may yield false positive results, including treatment with antibiotics such as piperacillin-tazobactam or amoxicillin clavulanate.[4,5] The clinical utility of the assay in non-neutropenic recipients is still being defined.

## Management

The management of invasive aspergillosis has evolved with the adoption of either preemptive or prophylactic strategies. Some centers treat patients with prophylactic mold-active oral triazoles until neutropenia has resolved. Other centers have adopted serial pulmonary CT scanning and galactomannan assays to try to identify invasive aspergillosis at early stages. Clinical trials to establish the optimal strategy are ongoing; however, adverse medication effects, medication interactions, and possible increases in the rate of invasive zygomycete infections are among the concerns that accompany long-term prophylactic strategies.[1,2]

Once the diagnosis of invasive aspergillosis has been established, several antifungal agents are available for treatment. Voriconazole was compared to amphotericin B deoxycholate in a direct comparison trial, and was shown to have a superior efficacy and toxicity profile.[1,6] Intravenous voriconazole includes a cyclodextrin vehicle that accumulates in patients with renal failure, and use of intravenous formulations in this setting should be used with caution. Lipid formulations of amphotericin B have fewer adverse effects than conventional amphotericin B, and allow for the infusion of higher doses. There are no studies directly comparing voriconazole with lipid formulations of amphotericin B, and many clinicians continue to favor the latter as initial therapy for invasive aspergillosis. Posaconazole is a triazole that is only available in oral formulations, and studies demonstrating efficacy are mostly limited to salvage treatment of invasive aspergillosis. Attention should also be given to the interactions between triazoles and other medications metabolized by the p450 system, particularly sirolimus and calcineurin inhibitors, such as tacrolimus or cyclosporine.

Echinocandins have in vitro and in vivo activity against most species of *Aspergillus,* and efficacy has been demonstrated for salvage therapy of invasive aspergillosis. Combination antifungal therapy has been used in some cases of refractory disease. In a retrospective analysis of patients who had progressive aspergillosis after treatment with liposomal amphotericin B, those who received voriconazole and caspofugin had improved outcomes when compared to those who received voriconazole alone.[3] This study, however, included comparison of groups of patients who were treated for different time periods. Randomized, controlled trials are ongoing to better define the role of combination therapy as initial treatment of invasive aspergillosis.

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 47-Year-Old Woman from Thailand with Worsening Dyspnea

**Chapter:** A 47-Year-Old Woman from Thailand with Worsening Dyspnea
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 47-year-old woman from Thailand, with a history 14 years prior to admission of orthotopic liver transplant for autoimmune hepatitis, presented with fevers, abdominal pain, diarrhea, and dry cough for 5 days. She had recently been admitted with jaundice, increasing liver transaminases, hyperbilirubinemia (14 mg/dl), and her liver biopsy showed chronic evolving graft rejection. She was born in Thailand but had lived in the United States for 20 years, and denied any recent travel, illicit drug use, animal contact, or contact with patients with tuberculosis. Her tuberculin skin test was negative less than one year ago.

On physical examination she was afebrile, with scleral icterus but in no acute distress. Laboratory values were significant for neutropenia (2.1 × $10^3$ WBC/µl) and elevated total bilirubin (16 mg/dl). Initially, her pulmonary examination and chest radiography were both unremarkable; however, over the next several days, her fevers progressed and she developed increasing cough and dyspnea. By hospital day 5, she was hypoxic with 85% oxygen saturation on ambient air, and increasingly tachypneic. Repeat chest radiography showed diffuse bilateral infiltrates (Figure **7d.1**) and chest CT showed diffuse bilateral ground-glass opacities with honeycombing (Figure **7d.2**). Direct fluorescent antibody (DFA) testing on a sputum sample was positive for *Pneumocystis jirovecii*. (Figure **7d.3**).

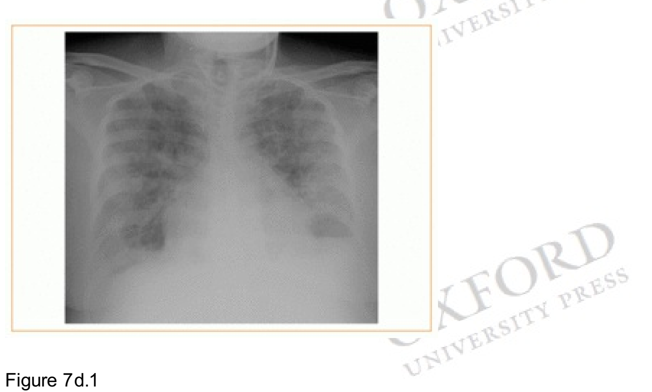




Figure 7d.1
Chest radiography, posterior-anterior view showing diffuse bilateral infiltrates.

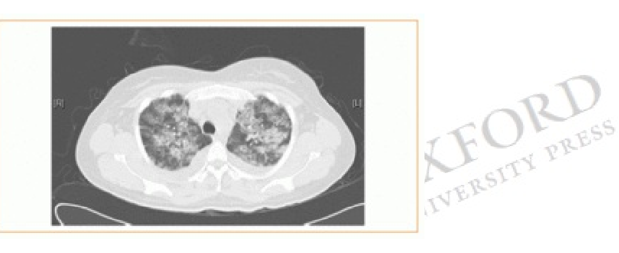


Figure 7d.2
Chest CT, axial view showing diffuse bilateral ground-glass opacities with honeycombing.

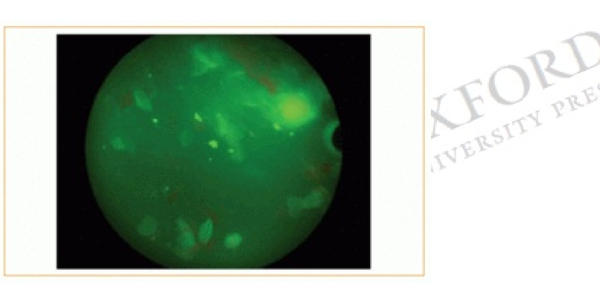




Figure 7d.3
Sputum sample positive with direct fluorescent antibody testing for *Pneumocystitis jirovecii*.

**Case 7d Discussion: *Pneumocystis jiroveci***

*Pneumocystis jirovecii*, formerly called *Pneumocystis carinii*, is an agent of pneumonia that is the most frequent opportunistic infection in patients with AIDS. In other immunocompromised patient populations, it has been less well-described, particularly in the post-transplant population. There are several differences in the epidemiology, clinical presentation, diagnostic methods, and mortality between HIV-positive and HIV-negative patients.

The number of patients with *Pneumocystis* pneumonia (PCP) in non-HIV-infected patients has steadily risen in the last decade. The majority of these infections have occurred in patients with hematologic malignancies or solid organ (such as kidney and liver) transplant recipients. In addition, 90% of these patients were reported to have been receiving steroids prior to the diagnosis of PCP.[2–4] In AIDS patients, PCP has classically presented as a subacute illness over several weeks in a patient with a CD4 count ( 200 cells/$mm^3$ with fever, dry cough, and dyspnea. Some patients, in fact, may be treated in an ambulatory setting.

In contrast, non-HIV-infected patients with PCP present more acutely over several days, with a more severe illness. Median CD4 counts in these patients vary greatly in the literature. In addition, the burden of organism is much greater in HIV-infected patients compared to non-HIV-infected patients, making diagnosis by GMS, Gram-Weigert, and DFA staining much more sensitive in the former, particularly on bronchoalveolar lavage (BAL) specimens. Our patient represents a rare case in which PCP was diagnosed on a single sputum sample via DFA. Other methods of diagnosis include polymerase chain reaction (PCR) of sputum or BAL specimens, though its positive predictive value (PPV) is much lower in non-HIV-infected patients compared to HIV-infected patients.[5]

Antimicrobial treatment for PCP, however, remains the same in both immunocompromised populations. Table 7d.1 lists first-line and alternative therapy based on the clinical severity of disease. A clear benefit of steroids for the treatment of PCP in AIDS patients who are hypoxic has been shown in the literature. The standard dose of prednisone is 40 mg twice daily over 5 days, then tapered over the ensuing 16 days of the illness. The benefit in non-HIV-infected patients has been less apparent. Few studies have been able to demonstrate a clear benefit to giving steroids in this population, with two major studies showing conflicting data.[6,7]

Table 7d.1 Management of *Pneumocystis* Pneumonia

| | |
|---|---|
| **Not Acutely Ill (Ambulatory setting)** | |
| FIRST LINE | |
| TMP/SMX | 1 DS tablet every 8 hours × 21 days |
| Dapsone + TMP | 100 mg orally every 24 hours + 5 mg/kg every 8 hours every 8 hours × 21 days |
| SECOND LINE | |
| Clindamycin + Primaquine | 300–450 mg orally every 6 hours + 15 mg base every 24 hours × 21 days |
| Atovaquone | 1500 mg orally every 24 hours × 21 days |
| **Acutely Ill** | |
| FIRST LINE | |
| TMP/SMX | 15 mg/kg/day IV divided every 6–8 hours × 21 days |
| SECOND LINE | |
| Clindamycin + Primaquine | 600 mg IV every 8 hours + 30 mg base orally every 24 hours × 21 days |
| Pentamidine | 4 mg/kg/day IV × 21 days |



Despite similar treatment regimens for PCP in both HIV-positive and HIV-negative patients, reported mortality rates between the two groups have differed widely, with the latter showing reports double that of the former. In addition, complication rates, including rates of respiratory failure and those requiring intensive care, have been higher in HIV-negative immunocompromised patients.[1–3]

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## Severe Pneumonia from a Gram-Positive Bacillus

**Chapter:** Severe Pneumonia from a Gram-Positive Bacillus
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 79-year-old man with a past medical history of myasthenia gravis presented with shortness of breath and cough for 3 weeks. He had been diagnosed with myasthenia gravis four months prior to presentation, and had been treated with prednisone and azathioprine. He was originally from Cuba, but had not traveled for several years, and he denied any fevers, chills, night sweats, or sick contacts. An admission chest radiograph at an outside institution revealed a left lower lobe infiltrate, and he was treated with broad-spectrum intravenous antibiotics for pneumonia. Because of progressive respiratory failure, he required intubation and mechanical ventilation. He was transferred to our institution for plasmapheresis for myasthenia gravis flare, and an infectious disease consultation was requested.

On physical examination, his temperature was 37.4°C with heart rate of 86 beats/minute and blood pressure of 121/65 mm/Hg. He was intubated, and had decreased breath sounds at the left base. Laboratory examination was significant for leukocytosis (13.4 $\times 10^3$ cells/µl, 94% neutrophils) and thrombocytopenia (80 $\times 10^3$ platelets/µl). Chest CT revealed multiple nodular infiltrates (Figure **7e.1**), a large left pleural effusion, and multiple air fluid collections consistent with left lower lobe empyema and abscess.



Figure 7e.1
Chest CT, axial view showing discrete left lower lobe nodular infiltrates.

Thoracotomy, pleural decortication, and wedge resection were performed, and the patient was found to have multiple abscesses, along with areas of necrosis and infarction in the lung parenchyma. Microscopic evaluation of the lung parenchyma revealed empyema, acute pneumonia, and multiples abscesses with filamentous bacillary forms visible on Gomori methenamine silver stained tissue (Figure **7e.2**). No organisms were visualized on Gram stain or acid-fast staining of the tissue, but cultures eventually grew Gram-positive bacilli that were initially misidentified as *Coryneform bacillus*. After further evaluation in the microbiology laboratory, cultures were correctly identified as *Nocardia asteroides* (Figures **7e.3** and **7e.4**), and the patient was treated with intravenous trimethoprim-sulfamethoxazole. The patient required tracheostomy for prolonged respiratory failure, but was eventually transferred to a rehabilitation facility after a 4-month hospitalization.

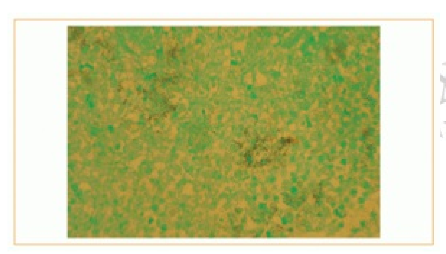




Figure 7e.2

Lung biopsy, Gomori methenamine silver stain showing abscesses with filamentous bacillary forms.



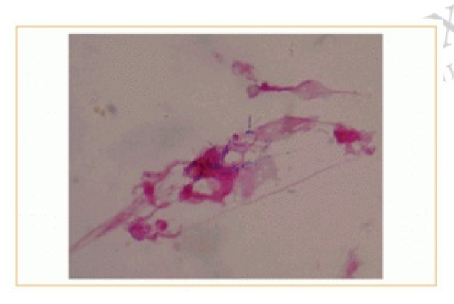


Figure 7e.3
Lung biopsy culture, Gram stain showing Gram-positive, beaded, branching bacilli later identified as *Nocardia asteroids*.

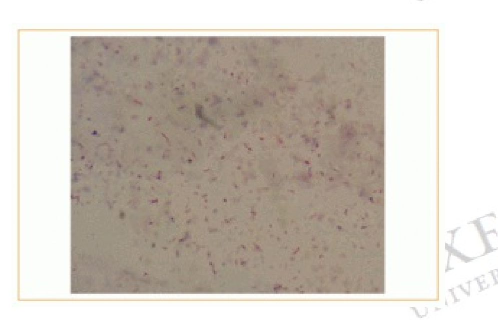


Figure 7e.4
Lung biopsy culture, Modified acid fast stain positive showing shorter bacillary forms of *Nocardia asteroides*.

**Case 7e Discussion: *Nocardia asteroides***

## Clinical Manifestations: Pulmonary Disease

*Nocardia* species are found in the environment in soil, organic matter, and water. They can cause both superficial and disseminated disease with resultant cutaneous, pulmonary, and central nervous system manifestations (see case 3c for discussion regarding classification, epidemiology, and management of CNS infections). Pulmonary disease is the most common manifestation (40% of patients with nocardiosis), and generally occurs in immunocompromised individuals.[1] Inhalation of dust particles is the most common route of acquisition, and men are three times as likely to be affected as women.[2] Almost 90% of pulmonary nocardiosis is caused by members of the *Nocardia asteroides* complex.[1]

Pulmonary nocardiosis can be an acute, subacute, or chronic infection, with both remissions and exacerbations. Patients at risk include those with chronic lung disease, such as COPD, and immunocompromised individuals—secondary to HIV, transplant, or prolonged treatment with immunosuppressive medications for autoimmune disorders.[3] Patients often present with a variety of symptoms and one observational study of 31 patients with pulmonary nocardiosis found that the most common clinical presentations were cough (77%), fever (71%), sputum production (65%), dyspnea (65%), chest pain (39%), and constitutional symptoms (42%).[4] Radiographic findings are also diverse and may include focal infiltrates, irregular densities, subpleural plaques, scattered nodules or masses which may or may not cavitate, single or multiple abscesses, and interstitial reticulonodular infiltrates.[2] Acute infections may progress to empyema in up to one-third of cases.[5] Because of the nonspecific radiographic findings, the initial differential diagnosis may include bacterial pneumonia, tuberculosis, fungal infections such as aspergillosis, and malignancy.[3] *Rhodococcus equi* infections can present a particular challenge because of the microbiologic similarities to *Nocardia* species (see below).

## Laboratory Diagnosis

Bronchoalveolar lavage fluid, sputum samples, abscesses, wound cultures, tissue biopsy, and cerebrospinal fluid are the most common specimens sent to the laboratory for diagnosis. The microbiology laboratory should be alerted when nocardiosis is suspected because routine laboratory and culture methods may fail to isolate the organism from normal commensal flora, and because *Nocardia* is a slow-growing organism.[3] While *Nocardia* will grow on standard blood culture media, initial growth can take 48–72 hours or longer; therefore, the laboratory should be asked to incubate cultures for at least three weeks. *Nocardia* species are catalase positive, and grow in the presence of lysozyme in a nutrient broth over a wide temperature range. Yield is increased by use of certain media, including Thayer-Martin agar with selective antibiotics in order to prevent the growth of more rapidly growing commensal flora that may obscure the diagnosis. The organism may also be isolated on Lowenstein-Jensen media (used for isolation of mycobacteria), Sabouraud's dextrose media (used for isolation of fungi), or buffered charcoal-yeast extract agar (used for growth of *Legionella* species).[2]

Typical colonies can be seen after 3–5 days and have a dry, chalky appearance, often produce aerial hyphae, and can have a "cotton candy" like appearance and an earthy odor. Direct smears show Gram-positive, beaded, branching filaments. The filaments may fragment to form rods or coccoid forms, giving the mistaken appearance typical of other bacterial forms, as in the case above. Other organisms with a similar appearance include *Actinomyces* species, *Rhodococcus equi*, and rapid-growing mycobacteria. When *Nocardia* is suspected on Gram stain, a modified Kinyoun technique using a weak acid (1% sulfuric acid) for decolorization can be done, as isolates are usually partially acid-fast.[2]

Biochemical methods are used for species identification, and involve the use of different metabolic reagents. The diagnosis of *Nocardia asteroides,* for example, is based on the hydrolysis of casein, tyrosine, xanthine, and hypoxanthine.[1] Newer molecular techniques such as PCR, restriction enzyme analysis, and 16S rRNA gene sequencing are useful for species confirmation, but are generally only performed in referral laboratories.[6]

## Management and Prognosis

Sulfonamides remain the drug of choice for pulmonary nocardiosis; however, because of increasing antimicrobial resistance, susceptibility testing should be performed. The Clinical and Laboratory Standard Institute (CLSI) has approved a standard susceptibility testing and interpretation method for *Nocardia* species.[6] Besides sulfonamides other antimicrobial classes with varying efficacy include carbapenems, fluoroquinolones, macrolides, oxazolidinones and aminoglycosides, and a combination of agents may be

indicated in severe cases. Mortality from pulmonary nocardiosis in some series has been reported as varying from 14%–40%; however, mortality with disseminated or CNS disease can approach 100%.[4] Duration of therapy should be prolonged, given the high rate of relapses: most experts recommend 6–12 months of therapy for immunocompetent patients, and one year for immunosuppressed patients. Given the high mortality rate and microbiologic challenges, clinical suspicion and early diagnosis are important factors in the management of pulmonary nocardiosis.

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## Fever, Cough, and Shortness of Breath in an Immunocompromised Host

**Chapter:** Fever, Cough, and Shortness of Breath in an Immunocompromised Host
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 52-year-old male with history of kidney transplantation secondary to hypertensive nephropathy presented to the emergency room complaining of fever, cough, blood-tinged sputum, and shortness of breath for one week. His cadaveric kidney transplant was three years prior to presentation, and his immunosuppressive medications included tacrolimus and mycophenolic acid. Antimicrobial prophylaxis with trimethoprim/sulfamethoxazole and valganciclovir had been discontinued a year prior, as recommended by his treating physician. On review of symptoms he admitted to an unintentional 15-pound weight loss over the prior month, as well as nausea and diarrhea for the preceding 3 days. He denied any other constitutional symptoms, and his last tuberculin skin test was negative prior to transplant. He was working as a school facilities inspector, and denied any recent travel history or sick contacts.

On physical examination he looked acutely ill, in moderate respiratory distress, and was febrile to 38.3°C, tachycardic (HR 124 beats/minute), tachypneic (RR 30 breaths/minute), and hypoxic (oxygen saturation 85% on ambient air). He had dry mucous membranes and deep bronchial breath sounds on the lower half of his right chest without dullness to percussion or egophony. Except for a well-healed scar on his abdomen, the rest of the physical examination was unremarkable.

His WBC was 22 × $10^3$/μl with 99% neutrophils, creatinine 3.3mg/dl, sodium 132 mEq/L, alanine aminotransferase 136 UI/mL, aspartate aminotransferase 135 UI/mL, total bilirubin 4 mg/dl, and direct bilirubin 3.5mg/dL. Chest radiography revealed a dense consolidation of almost the entirety of the right lung and a much smaller part of the left upper lobe (Figure **7f.1**), and chest CT confirmed severe bilateral pneumonia (Figure **7f.2**).

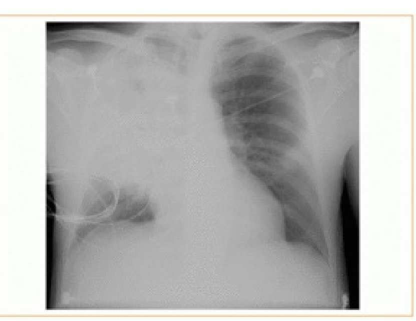


Figure 7f.1
Chest radiography, anterior-posterior view showing a dense consolidation of almost the entirety of the right lung and a much smaller part of the left upper lobe.



Figure 7f.2
Chest CT, axial view with severe bilateral pneumonia.

He was intubated on admission and underwent bronchoscopy with bronchoalveolar lavage (BAL). A urinary *Legionella* antigen test sent on admission came back positive on hospital day 2 (Figure **7f.3**), and direct fluorescence antibody (DFA) for *Legionella* of the BAL sample revealed apple green fluorescence around the alveolar cells (Figure **7f.4**) confirming the diagnosis of Legionnaire's disease. He was treated for 14 days with levofloxacin 500mg daily, became afebrile after 5 days, and was extubated after 10 days. He required intense rehabilitation and was discharged from the hospital one month after admission. Further questioning did not reveal any obvious exposures to possible contaminated water sources.






Figure 7f.3
Positive rapid urine *Legionella* antigen test.

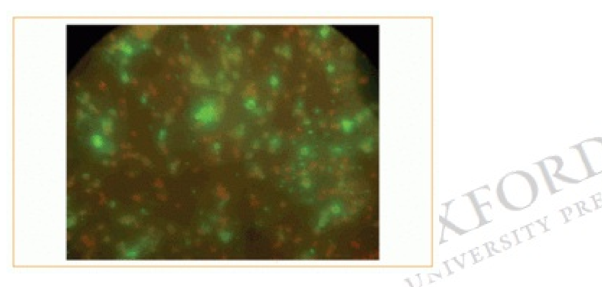


Figure 7f.4
Positive direct fluorescence antibody (DFA) stain for Legionella on bronchoalveolar lavage sample.

**Case 7f Discussion: *Legionella pneumophila***

## Microbiology and Epidemiology

*Legionella* was first identified in 1976 as the organism that caused an outbreak of pneumonia among attendants of the American Legion convention in Philadelphia. It comprises a family of ubiquitous intracellular Gram-negative coccobacilli that inhabit natural aquatic environments, manmade hot water systems, and air-conditioning/cooling towers. The survival of *Legionella* is aided by its parasitism of free-living amoebae, which encyst in environmental conditions that are not favorable for growth. The transmission of this organism is via inhalation of contaminated aerosols, or by microaspiration of contaminated water. There are more than 50 recognized species of *Legionella*, of which 20 have been recognized as human pathogens. *Legionella pneumophila* is by far the most common of these species to cause human disease, and serogroup 1 accounts for over 80% of the cases of legionellosis. The most frequently isolated non-*pneumophila* species include *longbeachae, bozemanae, micdadei, dumoffii, and feelii.*[1]

Legionnaire's disease accounts for 2% to 9% of the cases of community-acquired pneumonia, but it has also been associated with outbreaks in hospitals and long-term care facilities. Immunocompromised patients with defects in cell-mediated immunity are particularly susceptible to *Legionella* infection—e.g., corticosteroid use, hairy cell leukemia, and organ transplantation.[2,3] A retrospective study of 2946 solid organ transplant (SOT) patients in Spain found Legionnaire's disease in 0.5%, with a prevalence of 0.8% among heart recipients, 0.5% among kidney recipients, and 0.3% among kidney recipients. Of these patients, 21% had early onset disease (= 3 months after SOT) and 79% had late disease (= 3 months after SOT).[4]

In addition, severe *Legionella* pneumonia has been reported in association with the use of TNF-a antagonists such as infliximab and etanercept.[4] Cigarette smoking and chronic lung disease increase the risk of *Legionella* pneumonia, but patients with AIDS are not at increased risk of *Legionella* infection. Nonetheless; they tend to have more severe clinical illness when infected.[2]

## Clinical Features and Diagnosis

Two distinct clinical syndromes characterize *Legionella* infection: Legionnaire's disease classically presents with a moderate to severe pneumonia and multisystemic symptoms, whereas Pontiac fever is a mild, self-limited, flu-like syndrome without pulmonary findings. Legionnaire's disease has an incubation time of 2 to 10 days, and symptoms range from a mild cough and low-grade fever to stupor, respiratory failure, and multiorgan failure. Early in the illness, patients have nonspecific symptoms including fever, malaise, myalgias, anorexia, and headache. The temperature often exceeds 40°C, but the cough is typically only slightly productive. Gastrointestinal symptoms are prominent, especially diarrhea, which occurs in 20%–40% of cases.[1] Chest pain, occasionally pleuritic, can be prominent and when coupled with hemoptysis may mistakenly suggest other clinical entities such as pulmonary embolism. In a case series of 14 SOT patients with Legionnaire's disease,[4] the most common symptoms were chills (64%), fever (50%) and cough (50%).

Laboratory findings are nonspecific. Leukocytosis is often present, and in severe cases it may be accompanied by thrombocytopenia. Hyponatremia and hypophosphatemia

occur more frequently in Legionnaire's diseases than in other pneumonias. A mild to moderate elevation of liver enzymes is also commonly observed, and patients may develop acute kidney injury.[1] The radiographic findings of *Legionella* pneumonia can vary, and include unilateral or bilateral dense, patchy, or nodular pulmonary infiltrates that can progress to cavitation. Cavitary lung disease is relatively common in immunocompromised patients, particularly solid organ recipients, and pleural effusions are present in one-third of the patients.[5]

The gold standard for diagnosis of Legionnaire's disease is culture from a sputum or BAL specimen. This method has the advantage of being able to identify all *Legionella* species, and is 100% specific. The main disadvantages are that *Legionella* is difficult to culture, the method is time consuming, requiring up to 7 days to identify most colonies, and in many cases, patients have a nonproductive cough. In addition, *Legionella* requires buffered charcoal yeast extract agar supplemented with a-ketoglutarate medium for growth (BYCE), with a reported sensitivity ranging from 10%-80%.[5]

Measurement of acute and convalescent antibodies by IFA or ELISA to detect a fourfold rise in *Legionella* IgG titers is useful as an epidemiologic tool, but does not provide clinically applicable information for diagnosis of the acutely ill patient. One of the most useful methods is the detection of *Legionella pneumophila* Type 1 urinary antigen by EIA, which has a reported sensitivity of 60%–100% and a specificity of )99%. Several studies have shown that the sensitivity of the test is highest among patients with severe disease, and a rapid immunochromatographic test has a similar sensitivity and specificity. Antigenuria can be detected as early as one day after the onset of symptoms, and persists for weeks. The major disadvantage of the test is the inability to detect the other serogroups or species that comprise up to 20% of the cases of legionellosis.[5]

Direct fluorescent antibody (DFA) assay can be performed with polyclonal or monoclonal antibodies against *Legionella pneumophila*. The sensitivity of the test has been reported to be between 25%–85% with a specificity of 95%. Advantages of this test are that it is rapid and that it can detect species or serogroups other than *L. pneumophila* serogroup 1. The main disadvantage is that cross-reactivity with non-*legionella* bacteria, and background fluorescence, can decrease its performance. PCR is another diagnostic modality that has been applied to sputum, blood, and urine samples. Diagnostic PCR assays have principally targeted specific regions within 16S rRNA genes, the 23S-5S spacer region, 5S rDNA, or the macrophage inhibitor potentiator (mip) gene. In samples from the lower respiratory tract, PCR has shown a sensitivity equivalent to culture: however, false positive results have been reported.[5]

## Treatment

Mortality without treatment ranges from 16% to 30%, and with treatment it has been reduced to 5%–10% in patients with community-acquired disease. In one study of SOT patients, the mortality was found to be 14%, though large-scale studies of this population are lacking.[4] Fluoroquinolones, macrolides, rifampin, and tetracyclines are active against *Legionella*. Because *Legionella* is an intracellular organism, high intracellular levels of antibiotics favor bacterial killing. In immunocompetent patients, four small observational studies showed faster resolution of fever and shorter hospital stay with fluoroquinolones than with macrolides, but no difference in mortality rates. Newer macrolides, such as azithromycin 500 qd, and "respiratory" fluoroquinolones such as levofloxacin 500 qd, moxifloxacin 400 qd and gatifloxacin 400 qd, are currently recommended as the treatment of choice because of their potency and high intracellular concentration in the lungs. A 10-day to 14-day duration of antibiotics is usually sufficient in immunocompetent patients, but up to 21 days may be needed for immunocompromised patients with severe disease. In transplant recipients, fluoroquinolones are advantageous since some macrolides may inhibit the metabolism of immunosuppressant agents such as tacrolimus and cyclosporine.[3]

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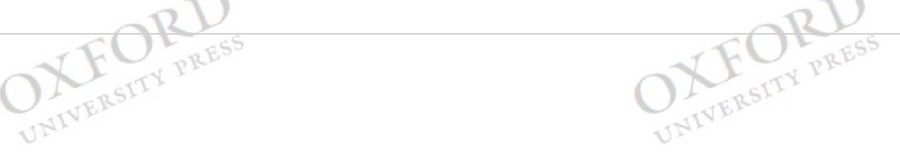







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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 36-Year-Old Man with Homonymous Hemianopsia

**Chapter:** A 36-Year-Old Man with Homonymous Hemianopsia
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0037

### Case Presentation

A 36-year-old man with a past medical history significant for non-insulin-dependent diabetes mellitus presented with abdominal pain, nausea, vomiting, and a low grade fever to 100.7° Fahrenheit. CT scan of the abdomen during that admission was significant for splenic infarctions, as well a wedge-shaped renal infarct (Figures **8a.1** and **8a.2**). A transesophageal echocardiogram was done to evaluate for a source of possible emboli, but no evidence of a vegetation was seen. One set of blood cultures was done and were negative. An evaluation for possible causes of hypercoagulability was pursued, and he was discharged on warfarin while results were pending.

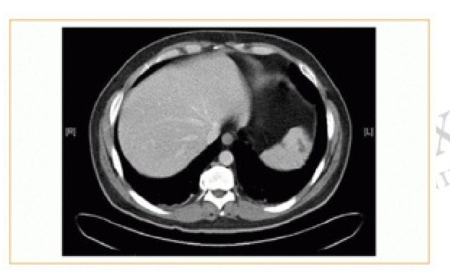


Figure 8a.1 CT
scan of the abdomen, axial view with splenic infarctions.





Figure 8a.2 CT
scan of the abdomen, axial view with multiple wedge-shaped renal infarcts.

One month later, he presented again to the emergency room with headache and visual complaints. He complained specifically of difficulty seeing out of the left eye and tunneled vision, and again reported some low grade fever and chills over the past month. He worked for the department of transportation and denied any recent sick contacts, pets, recent travel, dental extractions, or intravenous drug use.

On physical examination in the emergency room, his vital signs were 38.6° Farenheit and he was tachycardic to 119 beats per minute, with a blood pressure of 145/69. He had anisocoria (right pupil 4mm, left pupil 3mm)and left homonymous hemianopsia; visual acuity was 20/50 bilaterally. His extraocular movements were intact, and facial movements were symmetric. His reflexes were 2+ throughout, though slightly brisker on the right side than on the left. He had a soft diastolic murmur on cardiac exam, but the remainder of his physical examination was unremarkable.

Laboratory examination was significant for leukocytosis (13.6 x 10 WBC/μl, 81% neutrophils), elevated erythrocyte sedimentation rate (105 mm/hour), CRP (55, nl range 0–8), and therapeutic INR (2.7). A non-contrast head CT scan and MRI showed multiple hemorrhagic infarcts, including 3.8 cm hemorrhage within the right posterior parietal lobe and 6 mm hemorrhage in the right temporal lobe, and 1.9 cm hemorrhage in the left occipital lobe (Figures **8a.3** and **8a.4**). He was admitted to the neurology service for management of intracranial hemorrhage.

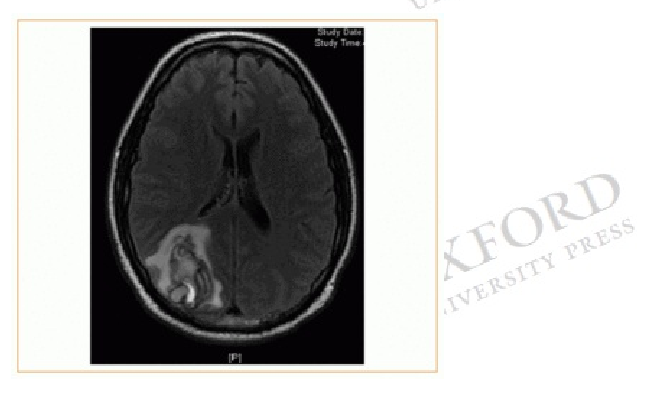




Figure 8a.3
MRI brain, axial view showing 3.8 cm hemorrhagic infarct within the right posterior parietal lobe.



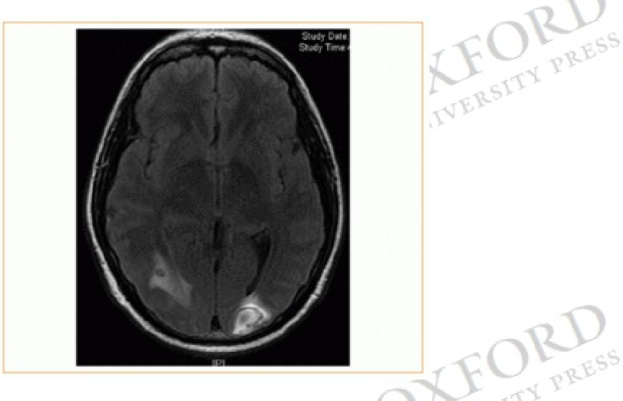






Figure 8a.4
MRI brain, axial view showing 1.9 cm hemorrhagic infarct in the left occipital lobe.

A repeat transesophageal echocardiogram showed a small mobile mass on the noncoronary cusp of the aortic valve and abscess on the anterior leaflet of the mitral valve, with mild to moderate aortic regurgitation, mild mitral regurgitation and mildly decreased left ventricular systolic function of 40%(Figure **8a.5**). Blood cultures were drawn and grew *Streptococcus constellatus* from four different sets; penicillin MIC was 0.06 (Figure **8a.6**). He was started on ceftriaxone 2 grams IV daily for 4 weeks, and his visual deficit improved to a minor left inferior quadrantanopsia.

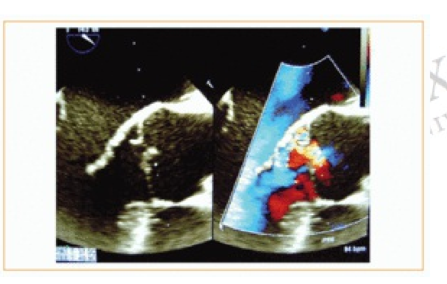


Figure 8a.5
Transesophageal echocardiogram showed a small mobile mass on the non-coronary cusp of aortic valve and abscess on anterior leaflet of mitral valve with mild to moderate aortic regurgitation, mild mitral regurgitation and mildly decreased left ventricular systolic function of 40%.





Figure 8a.6
Blood cultures with Gram-positive cocci in chains, later identified as *Streptococcus constellatus*.

He was discharged and readmitted after 4 weeks of intravenous antibiotics for valve replacement and repair. In the operating room, he had vegetations on the noncoronary and right coronary cusps of the aortic valve, and the aortic valve was excised. An abscess cavity was also seen on the ventricular surface of the mitral valve which was debrided and the mitral valve was repaired. The aortic valve was replaced with a St. Jude's mechanical valve. Gram-stain of the mitral valve abscess showed few Gram-positive cocci in pairs, but final cultures were negative. The microscopic examination of the excised valves was consistent with healing vegetations of infectious endocarditis. The patient had no further complications, and was discharged to complete 4 more weeks of intravenous ceftriaxone.

**Case 8a Discussion: *Streptococcus constellatus* Endocarditis**

## Diagnosis

The diagnosis of infective endocarditis (IE) can be straightforward in many patients with classical clinical manifestations; in other cases, such as the patient described above, it may initially be more challenging. The Duke criteria, described by Durack and colleagues in 1994, are most commonly used by most clinicians in the diagnosis of IE. Diagnosis is based on the presence of either major or minor clinical criteria. Major criteria include echocardiographic data or positive blood cultures with typical microorganisms, including *Staphylococcus aureus,* viridians streptococci, *Streptococcus bovis*, HACEK group, or community-acquired enterococci. Minor criteria include fever, immunologic phenomena, vascular phenomena, a positive blood culture with an organism not meeting one of the major criteria, or predisposing condition. Criteria for diagnosis of clinically definite IE include 2 major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria (see Table 8a.1). Several studies of the Duke criteria have consistently shown high sensitivity and specificity in diagnosis of IE.[1]

| Table 8a.1 (taken from Baddour et al, *Circulation* 2005) |
|---|
| **Major criteria**<br>Blood culture positive for IE<br>Typical microorganisms consistent with IE from separate blood cultures: Viridians streptococci, *Streptococcus bovis*, HACEK group, ***Staphylococcus aureus***; or community-acquired enterococci in the absence of a primary focus; or<br>Microorganisms consistent with IE from persistently positive blood cultures defined as follows: At least 2 positive cultures of blood samples drawn >12 h apart; or all of 3 or a majority of =4 separate cultures of blood (with first and last sample drawn at least 1 h apart)<br>**Single positive blood culture for Coxiella burnetii or anti-phase 1 IgG antibody titer >1:800**<br>Evidence of endocardial involvement<br>Echocardiogram positive for IE **(TEE recommended for patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients)** defined as follows: Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; new valvular regurgitation (worsening or changing or preexisting murmur not sufficient) |
| **Minor criteria**<br>Predisposition, predisposing heart condition, or IDU<br>Fever, temperature >38°C<br>Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjuctival hemorrhages, and Janeway's lesions<br>Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor<br>Microbiological evidence: positive blood culture but does not meet a major criterion as noted above* or serological evidence of active infection with organism consistent with IE<br>**Echocardiographic minor criteria eliminated** |

Modifications shown in boldface.

* Excludes single positive for coagulase-negative staphylococci and organisms that do not cause endocarditis.

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Both microbiological and echocardiographic data are central to the diagnosis of IE, as described by the Duke criteria above. At least three sets of blood cultures should be taken in the first 24 hours. If the patient has received any antibiotics in the preceding two weeks, more specimens may be necessary. Since the bacteremia is usually continuous and low grade, the first two blood cultures reveal the etiologic agent more than 90% of the time.[2]

Echocardiography should also be performed in patients with suspected endocarditis. Evidence of an oscillating mass or vegetation, an annular abscess, prosthetic valve partial dehiscence, or new valvular regurgitation, meet major echocardiographic criteria for IE. Whether transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) is performed first may depend on the clinical scenario. TTE is often not a sensitive as TEE for the detection of vegetations on posterior valves (aortic and mitral) and therefore a negative test does not exclude left-sided IE. In addition, it may be less adequate in cases of obesity, COPD, or chest wall deformities. It does, however, have a high sensitivity for detecting right-sided endocarditis, since the pulmonic and tricuspid valves are more anterior structures.[1]

Transesophageal echocardiography is more sensitive than TTE in the detection of vegetations, especially in prosthetic valves. Studies have reported sensitivities of 48%–100% for TEE as compared with 18%–63% in TTE; however, a negative result on TEE also does not exclude endocarditis. There may be false negatives in the case of small vegetations, and vegetations that may have already embolized. In cases of high clinical suspicion such as the patient described above, TEE should be repeated in 7–10 days. In such cases, an increase in the vegetation size or presence of abscess cavity may become visible.[1]

## Management

The microorganisms that are most commonly responsible for IE include those of the *Streptococcus* and *Staphylococcus* genera. While *Staphylococcus aureus* has developed increasing importance in recent years, the most common cause of endocarditis has traditionally been members of the *Streptococcus* genus. Specifically, the viridians group streptococci cause the most cases of IE, accounting for 30%–40% of all infective endocarditis. Usually the presentation is subacute, and may present with nonspecific symptoms as described in the case above; 20% of cases come to attention because of embolic phenomena.[2]

Viridans group streptococci are facultatively anaerobic, Gram-positive cocci that do not produce catalase or coagulase. They are usually alpha-hemolytic, but can rarely be beta-hemolytic. The term *viridans* comes from the greenish discoloration on blood agar caused by partial destruction of erythrocytes. They are associated with the GI tract, most commonly as a part of normal human oral commensal flora. The viridians group streptococci have undergone multiple changes in taxonomy and naming, but the most clinically significant species can be assigned to one of the following groups: the *anginosus* group, the *mitis* group, the *mutans* group, the *salivarius* group, and the *sanguinis* group.

Members of the *anginosus* group, also known as the *Streptococcus milleri* group, include *Streptococcus intermedius, constellatus* and *anginosus*. The *Streptococcus anginosus* group is known for causing abscesses and hematogenously disseminated infections. The nutritionally variant streptococci, specifically *Gemella,* are also known for causing endocarditis, as is the Group D, nonenteroccocal *Streptococcus* associated with colon malignancy, *Streptococcus bovis.*[2]

Antibiotic therapy for infective endocarditis caused by the viridans group streptococci is guided by the penicillin minimal inhibitory concentration (MIC). For highly penicillin-susceptible strains (PCN MIC ( 0.12 μg/ml), there are four possible options. These include intravenous penicillin or ceftriaxone for 4 weeks, penicillin or ceftriaxone plus gentamicin for 2 weeks, or vancomycin. Previous studies have shown that the synergistic addition of gentamicin allows for shortening the duration of therapy with equivalent cure rates; however, patients require careful monitoring for potential ototoxicity or nephrotoxicity. For strains relatively resistant to penicillin with an MIC of 0.12 to 0.5 μg/ml, treatment options include intravenous penicillin or ceftriaxone for 4 weeks with single daily-dose gentamicin for 2 weeks, or vancomycin. For resistant viridians streptococci, treatment requires 4–6 weeks of intravenous penicillin and gentamicin or vancomycin.[1]

## Complications

Surgical intervention in patients with infective endocarditis is indicated in certain clinical scenarios. Patients with infective endocarditis and congestive heart failure have a higher mortality when treated with medical therapy alone, and should undergo valve replacement or repair. In addition, other indications for surgical management include fungal endocarditis, persistent infection or bacteremia, evidence of one or more embolic events during the first 2 weeks of therapy, vegetations larger than 10 mm on the anterior mitral valve leaflet, echocardiographic evidence of valve dehiscence, perforation, rupture or fistula, or a large perivalvular abscess' [3,4]

In this case, the patient had evidence of both perivalvular abscess and multiple embolic events, which were an indication for surgical valve replacement. Perivalvular abscess may be difficult to diagnose even by TEE. This complication occurs more in aortic IE, and can often result in AV heart block—a finding with a high positive predictive value for abscess formation. Acute surgery is beneficial in these patients to prevent further deterioration of cardiac function.[4]

Embolic events occur in 10%–50% of cases and often involve the lungs, coronary arteries, spleen, bowel, and extremities. Up to 50%–65% of embolic events involve the central nervous system and include stroke or mycotic aneurysm. Prediction of embolic events can be difficult; in some studies, size of vegetation appears to correlate with risk of embolization, but other studies have shown this not to be the case. Mitral valve vegetations do appear to carry a greater risk of embolization than aortic valve vegetations, and an increase in vegetation size over 4–8 weeks also appears to carry a greater risk of embolization.[4] The timing of surgical intervention in these patients is often complicated by the concern for conversion of an ischemic stroke to hemorrhagic stroke, secondary to cardiopulmonary bypass during surgery and postoperative anticoagulation. Therefore, surgery is often delayed at least 10–14 days in such patients. Decisions in each case need to be individualized, and should be made in conjunction with cardiothoracic surgeons, neurologists, and infectious disease specialists.

## Prophylaxis

Guidelines for the prevention of infective endocarditis were recently updated in 2007. Previous guidelines stratified risk for infective endocarditis based on high, moderate, or low risk cardiac conditions and also provided a list of dental, GI, GU, and respiratory procedures for which prophylaxis was and was not indicated; however, more recently the guidelines have been revised to reflect more evidence-based literature. The revisions were made based on the premise that endocarditis is likely to result more from bacteremia associated with daily activities, rather than bacteremia associated with dental care or GI/GU procedures, and that antibiotic prophylaxis may only prevent a very small number of cases of IE after such procedures. In addition, the newer guidelines emphasize that routine dental care was more important in preventing IE, rather than antibiotic prophylaxis, and that the risk of antimicrobial therapy may exceed any possible benefit, if any existed.[5]

The current guidelines suggest that endocarditis prophylaxis only be recommended in patients with certain cardiac conditions in which the highest risk of adverse outcomes from IE exists. These include patients with a prosthetic cardiac valve, or where prosthetic material was used for a cardiac valve repair, those with a history of IE or congenital heart disease, and cardiac transplant patients who develop cardiac valvuloplasty.[5] As no randomized controlled trial or convincing data exists demonstrating that antibiotic prophylaxis prevents IE associated with bacteremia after an invasive procedure, these guidelines were revised to recommend prophylaxis only in those patients in whom the development of IE would be more likely to lead to an adverse outcome, and not necessarily based on an increased lifetime risk of acquiring IE.

Antibiotics for prophylaxis should be administered as a single dose prior to the procedure; administration of the dose after the procedure should only be indicated in patients who did not receive their dose prior to the procedure. As bacteremia may result from minor manipulations or dental work, dental prophylaxis is recommended in the groups listed above when undergoing any dental procedure involving manipulation of the gingival or periapical region of the teeth, or perforation of the oral mucosa. Amoxicillin is the drug of choice given that it is well absorbed in the GI tract and achieves high serum concentrations. Other alternatives in penicillin-allergic patients include first-generation cephalosporins, clindamycin, or macrolide antibiotics.[5] These antibiotics are chosen for their low cost, wide availability, and activity against viridians group streptococci; however, the effect of the development of recent resistant strains of viridians group streptococci is unknown and should not impact the drug chosen for prophylaxis.

Lastly, antibiotic prophylaxis is deemed reasonable by the revised guidelines in patients undergoing respiratory invasive procedures in which incision or biopsy of the respiratory mucosa is performed; i.e., bronchoscopy with biopsy. The administration of antibiotics to prevent IE in patients undergoing GI or GU procedures is no longer recommended. In patients undergoing a surgical procedure involving infected skin, soft tissue, or musculoskeletal tissue, the guidelines recommend antibiotics with activity against *Staphylococcus aureus* and B-hemolytic *Streptococcus*. For further circumstances and exceptions, please see the guidelines for prophylaxis of infective endocarditis referenced below.[5]

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## Shortness of Breath and Weight Loss in a Patient with Hypertrophic Obstructive Cardiomyopathy

**Chapter:** Shortness of Breath and Weight Loss in a Patient with Hypertrophic Obstructive Cardiomyopathy
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0038

### Case Presentation

A 34-year-old man was admitted with 3 days of worsening shortness of breath, four-pillow orthopnea, and left-sided chest pain. Three months prior to admission, he was evaluated for a longstanding history of dyspnea on exertion and palpitations. At the time, an echocardiogram revealed an asymmetrically thickened septum, along with borderline left-ventricular outflow obstruction and mild mitral regurgitation with systolic anterior motion. He was diagnosed with hypertrophic obstructive cardiomyopathy and was treated with a beta-blocker. Over the next 3 months his symptoms gradually worsened, and he unintentionally lost 40 pounds, but denied fevers, chills or night sweats. During the days prior to admission, his symptoms acutely exacerbated and he was admitted electively for a cardiac catheterization and alcohol ablation of the interventricular septum.

Before the procedure was performed, a repeat echocardiogram revealed a new vegetation on the anterior leaflet of the mitral valve, along with new severe mitral regurgitation. On admission he was afebrile, and his physical examination was notable for bibasilar crackles, a loud 4/6 systolic murmur, and a laterally displaced apex, but no jugular venous distention or peripheral edema. His oropharyngeal exam was unremarkable and his dentition did not appear to hold gross pathology. Laboratory analyses revealed leukocytosis (15.6 × $10^3$ WBC/ul, 80% neutrophils), anemia (hemoglobin 11.4 g/dl), and mildly elevated liver enzymes (ALT 143 IU/L, AST 96 IU/L). Blood cultures drawn on admission grew *Cardiobacterium hominis* after fifty-four hours of incubation (Figure **8b.1**). He later revealed that he had undergone dental extraction 4 months prior to admission. The patient underwent mitral valve replacement and septal myomectomy. Gram stain of the mitral valve showed gram-negative bacilli but the valve culture was sterile, and he was discharged home to complete 6 weeks of intravenous ceftriaxone.

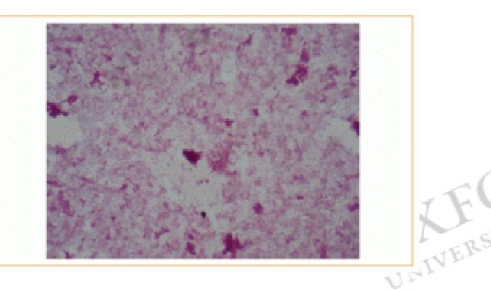




Figure 8b.1
Gram stain showing *Cardiobacterium hominis*.

#### Case 8b Discussion: *Cardiobacterium hominis* Endocarditis

#### Clinical Features and Diagnosis

*Cardiobacterium hominis* is Gram-negative bacillus that often appears as pairs, short chains, teardrops, rosettes or clusters.[1] Although it is part of the normal oropharyngeal flora, it can cause endocarditis in patients with (76%) or without (24%) predisposing heart conditions.[2] It is often classified as part of the HACEK group of oropharyngeal bacteria, together with *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus,* and *Haemophilus paraphrophilus), Aggregatibacter actinomycetemcomitans* (formerly known as *Actinobacillus*)*, Eikenella corrodens,* and *Kingella species* (*Kingella kingae and Kingella denitrificans).* These organisms grow slowly in standard blood culture media, and they account for part of the cases of culture-negative endocarditis.

Culture-negative endocarditis is a broad term that groups together organisms such as HACEK, but also includes *Coxiella burnetti*, *Bartonella spp.* and several other fastidious organisms. Nonetheless, the most common cause of culture-negative endocarditis is, undoubtedly, partially treated staphylococcal or streptococcal infections[3] (Table 8b.1). The yield of growth of HACEK organisms can be increased by holding blood cultures for a prolonged period of time, ≥ 2 weeks being typically recommended, and their growth is enhanced by the presence of increased carbon dioxide tension.[4] Nonetheless, in a study published in the late 1990s, the mean time to growth was found to be 3.3 days, with

most organisms growing by day 10.[5] Most modern laboratories have greatly improved their culture techniques, but unfortunately, there is no new published data looking at the growth yield since then. More recently, some laboratories have successfully reported the use of PCR and gene sequence analysis of the 16S rRNA of the organisms as a means to identify HACEK organisms in both blood and valve tissue.[6–8]

Table 8b.1 Bacteria Associated with CNE

| **Bacteria** | **Number of published cases** |
|---|---|
| *Staphylococcus* spp | Principle cause |
| *Streptococcus* spp | 2nd most common |
| *Enterococcus* spp | 3rd most common |
| *Pseudomonas aeruginosa* | Frequent in IV drug abusers |
| *Coxiella burnetii* | 485 |
| *Bartonella* spp | 252 |
| *Corynebacterium* spp | 201 |
| *Brucella* spp | 155 |
| *Abiotrophia* spp | 120 |
| *Neisseria* spp | 119 |
| *Actinobacillus actinomycetemcomitans** | 103 |
| *Haemophilus aphrophilus** | 80 |
| *Cardiobacterium hominis** | 80 |
| *Listeria monocytogenes* | 73 |
| *Haemophilus parainfluenzae* | 72 |
| *Erysipelothrix* spp | 65 |
| *Gemella* spp | 44 |
| *Pasteurella* spp | 33 |
| *Kinglella kingae** | 33 |
| *Eikenella corrodens** | 25 |
| *Mycobacterium* spp | 23 |
| *Capnocytophaga* spp | 23 |
| *Campylobacter* spp | 20 |
| *Yersinia* spp | 15 |
| *Mycoplasma* spp | 13 |
| *Granulicatella* spp | 13 |
| *Legionella* spp | 9 |
| *Tropheryma whipplei* | 9 |

* Organisms belonging to the HACEK group.

CNE—culture-negative endocarditis; IE—infective endocarditis; IV—intravenous.

With kind permission from Springer Science+Business Media: Madico GE, Rice PA. 16S-Ribosomal DNA to Diagnose Culture-Negative Endocarditis. *Curr Infect Dis Rep.* 2008;10(4):280–286. Table 1.

The prevalence of HACEK endocarditis remains low across different communities. In a study from Olmstead County, Minnesota the HACEK group accounted for 3% of the cases of community-acquired native valve endocarditis and 6% of the referral population.[9] A more recent study from Argentina[10] showed a prevalence of 6%. Factors such as

the number of intravenous drug users and circulating local flora including the prevalence of community-acquired methicillin resistant *Staphylococcus aureus*, might affect the prevalence of HACEK infections.

The largest published case series of HACEK endocarditis showed that of 45 confirmed cases, 19 (42%) grew *Haemophilus* spp.; 9 (20%) *Actinobacillus actinomycetemcomitans*; 12 (27%) *Cardiobacterium hominis*; 2 (4%), *Eikenella corrodens*; and 3 (7%) *Kingella kingae.* Almost all of these patients had fever as a presenting symptom (98%), followed by a new or changing murmur (78%), microemboli (67%), splenomegaly (51%), and macroemboli (7%). Of this group, 39 (87%) had prior structural heart disease or a prosthetic valve, 9 (20%) had poor dentition, and 17 (38%) had undergone prior dental work. Twenty patients (45%) had aortic valve involvement and 20 (45%) had mitral valve involvement. Both valves were involved in only 2 cases (4%). Overall, 2 patients died (2%), with 18 (40%) requiring surgery.[5]

## Treatment

Previously, the HACEK group was uniformly susceptible to ampicillin; however, β-lactamase producing strains of HACEK are appearing with increased frequency. Acknowledging that there is limited published data supporting a specific treatment or duration, the American Heart Association released a set of guidelines, which has been endorsed by the Infectious Disease Society of America, recommending ceftriaxone or ampicillin-sulbactam as first-line therapy.[11] The HACEK group is susceptible in vitro to fluoroquinolones, but there are only a few case reports of the use of this class of antibiotics for endocarditis treatment; therefore, fluoroquinolones are only recommended for patients who cannot tolerate β-lactams.

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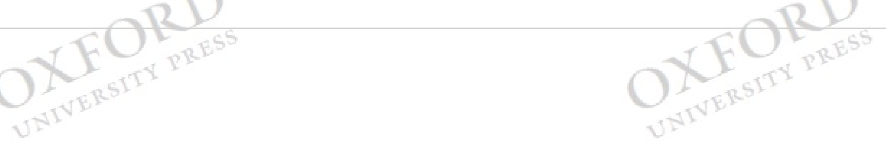







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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 24-Year-Old Man from Botswana with Pleuritic Chest Pain

**Chapter:** A 24-Year-Old Man from Botswana with Pleuritic Chest Pain
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 24-year-old African student presented to a local emergency department with a one week history of lower back pain, fever, chills, shortness of breath, and pleuritic chest pain. The patient had recently immigrated to the United States from Botswana, one month prior to presentation. He had been treated for malaria approximately 10 years ago, but otherwise had no significant medical history. His review of systems was also notable for decreased appetite and a mild nonproductive cough. On physical examination, he was a thin male in no acute distress, whose blood pressure was 94/57 and whose oxygen saturation was 97% on ambient air. His physical exam was otherwise unremarkable, but a chest radiograph revealed an enlarged cardiac silhouette (Figure **8c.1**).






Figure 8c.1
Chest radiography anterior posterior view showing an enlarged cardiac silhouette.

Echocardiography revealed a large pericardial effusion with early cardiac tamponade, and a pericardiocentesis was performed. Pericardial fluid analysis revealed protein 5.6, glucose 44, LDH 423, WBC 4144 (62% lymphocytes, 32% polymorphonuclear cells), and the direct smear of the pericardial fluid was negative for acid-fast bacilli. The patient felt better after the pericardiocentesis, but his fevers persisted. HIV serology, malaria smears, blood cultures,and sputum for acid-fast bacilli were all negative. Pericardial biopsy did not reveal granulomas; however, cultures of pericardial fluid and tissue later grew *Mycobacterium tuberculosis* complex (MTB), and the patient was treated with rifampin, isoniazid, pyrizinamide, and ethambutol.

#### Case 8c Discussion: Tuberculous Pericarditis

#### Epidemiology

Tuberculous pericarditis is a rare manifestation of tuberculosis that can be fatal even with proper diagnosis and treatment. The incidence of this form of tuberculosis has declined in the United States but it is reemerging in areas with significant populations of recent immigrants from endemic countries.[1] It remains an especially important problem in countries with high HIV prevalence. One study from Tanzania enrolled 28 patients with large pericardial effusions, and of the 14 patients who were HIV positive, all had tuberculous pericarditis.[2]

Pericardial infection with *Mycobacterium tuberculosis* may occur via extension of infection from the lung, tracheobronchial tree, adjacent lymph nodes, spine, and sternum, or via miliary spread. In most adults, pericardial tuberculosis represents reactivation of the disease, and the primary pulmonary focus may not be apparent.

#### Clinical Manifestations and Diagnosis

The symptoms of tuberculous pericarditis are nonspecific, and diagnosis may be delayed or missed because of the challenges of confirming this manifestation of TB. Patients may present with acute pleuritic chest pain, or with more insidious symptoms suggesting heart failure, such as cough, dyspnea, and orthopnea. Typical systemic symptoms of tuberculosis such as night sweats, fever, and weight loss may also be present. Physical findings of TB pericarditis include fever, pulsus paradoxus, pericardial rub, hepatomegaly, and internal jugular vein distention. In areas of high endemicity, symptoms and signs of pericarditis may be enough to prompt empiric therapy because most of the cases of exudative pericarditis are secondary to tuberculosis.[2]



A positive tuberculin skin test result may increase the suspicion of TB pericarditis, but a negative skin test result does not exclude the diagnosis.

Nontraumatic hemopericardium is most suggestive of tuberculous or malignant etiologies. In most patients with TB pericarditis, the fluid is exudative, with a leukocyte count ranging from 700–54,000/μl. Examination of smears of pericardial fluid has poor sensitivity, and cultures are positive in less than 50% of cases.[3]

Pericardial biopsy with tissue sent for both culture and histopathological examination is the diagnostic procedure with the highest yield (Figure **8c.2 and 8c.3**). Adenosine deaminase (ADA) levels and measurement of interferon gamma levels in pericardial fluid are adjunctive studies that can be useful. The sensitivity of elevated IFN is 92%, that of elevated ADA is 87%, and their specificities are 100% and 89%, respectively.[4]

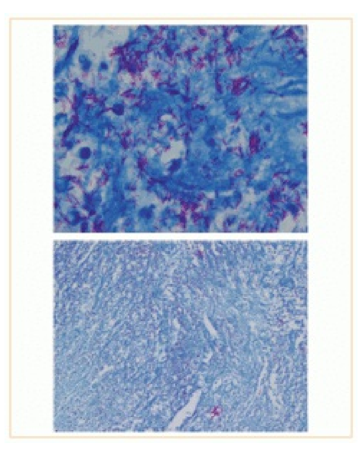




Figure 8c.2 and 8c.3
Oil immersion and low power view of the pericardium stained with Fites stain showing *Mycobacterium tuberculosis*.

Reuter et al. suggested a classification tree for diagnosis of tuberculous pericarditis based on pericardial fluid ADA and interferon gamma levels (Figures **8c.4** and **8c.5**).[4] PCR for mycobacterial DNA has been used for diagnosis of pericardial TB, but its sensitivity has been reported to be as low as 30% in a study in an endemic area.[4]

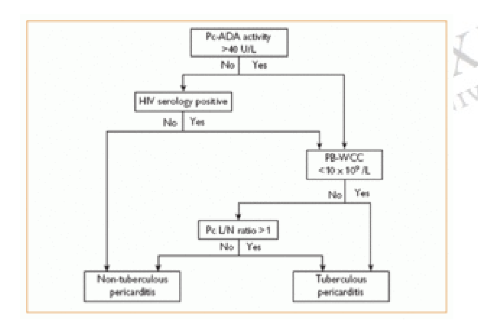



Figure 8c.4
Classification tree developed for the diagnosis of pericardial TB based on Pc-ADA, pericardial adenosine deaminase; PB-WCC, peripheral blood white cell count; Pc L/N ratio, pericardial lymphocyte/neutrophil ratio. Reprinted with permission from Reuter H, Burgess L, van Vuuren W, Doubell A. Diagnosing tuberculous pericarditis. *QJM*. 2006; 99(12): 827–839.

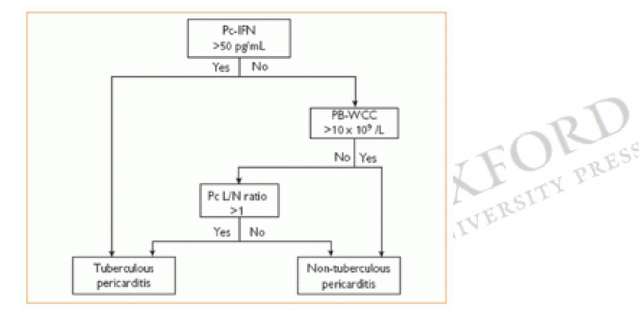





Figure 8c.5
Classification tree based on the determination of IFN-gamma levels for the diagnosis of pericardial TB. Pc-IFN, pericardial interferon-gamma; PB-WCC, peripheral blood white-cell count; Pc L/N ratio, pericardial lymphocyte/neutrophil ratio. Reprinted with permission from Reuter H, Burgess L, van Vuuren W, Doubell A. Diagnosing tuberculous pericarditis. *QJM*. 2006;99(12):827–839.

## Management

The treatment of most extrapulmonary manifestations of tuberculosis, such as tuberculous pericarditis, is the same as pulmonary tuberculosis (see Chapter 6 for full discussion). If cultures are positive for *Mycobacterium tuberculosis* that is susceptible to isoniazid and rifampin, 2 months of treatment with isoniazid, rifampin, pyrazinamide, and ethambutol is followed by an additional 4 months of isoniazid and rifampin. The addition of corticosteroids is recommended during the first 11 weeks of treatment in order to decrease the likelihood of late constrictive pericarditis. In one study, the addition of corticosteroids reduced mortality and the need for subsequent pericardiectomy.[5] Pericardiectomy is generally reserved for patients who remain hemodynamically compromised after 4–6 weeks of adequate therapy.[3,5]

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## Skin Lesion in a Patient with Recent Heart Transplant

**Chapter:** Skin Lesion in a Patient with Recent Heart Transplant
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 53-year-old man with a history of dilated cardiomyopathy (DCM) underwent heart transplantation 2 months prior to presenting with left lower extremity pain, swelling and erythema. Two weeks prior to admission, he noticed pain and swelling in his left ankle, and a few days later he noticed an area of skin ulceration that had steadily grown larger. He was treated with cephalexin for a presumed cellulitis, and colchicine for a possible diagnosis of gout without improvement. He had subjective fevers and a measured temperature of 101.7° F one day prior to admission.

His past medical history was notable hypertension and diabetes, and his medications included mycophenolate, tacrolimus, prednisone, trimethoprim/sulfamethoxazole, valganciclovir, insulin, furosemide, calcium, ferrous sulfate, and diltiazem. The patient was from a small rural village in El Salvador, but he had lived United States for 10 years prior to admission. On physical examination, he was afebrile, and on the left ankle there was a 2cm area of swelling, ulceration, and erythema over the left lateral malleolus (Figure **8d.1**). There were also painful nodules on the calf proximal to the skin ulcer (Figure **8d.2**). The remainder of the physical examination was unremarkable.



Figure 8d.1
Physical examination revealed a 2cm area of swelling, ulceration and erythema over the left lateral malleolus.





Figure 8d.2
Physical examination revealed painful nodules on the calf proximal to the skin ulcer.

Laboratory analyses were notable for anemia (8.8 mg/dl) and renal insufficiency (creatinine 2.5mg/dl), but the white blood cell count, platelets, liver function panel, and serum electrolytes were within normal limits. A plain radiograph of the left ankle showed no evidence of fracture, periosteal reaction, or joint space disease. After 48 hours of treatment with vancomycin, the patient had no obvious improvement in his symptoms. Intravenous acyclovir was initiated for the possibility of an atypical presentation of herpes zoster in

the setting of valganciclovir prophylaxis; however, there was no improvement and biopsy was recommended to assess for another opportunistic pathogen, such as a mycobacterium, fungus, *Nocardia*, or a parasitic infection, such as Chagas' disease. A biopsy of the lesions was performed, revealing the presence of the amastigotes of *Trypanosoma cruzi* at the dermal–epidermal junction (Figure **8d.3**).

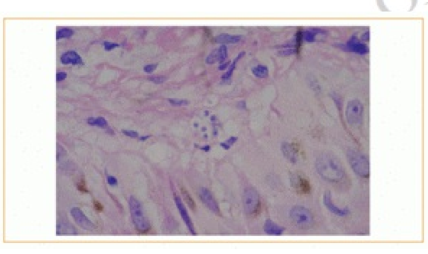


Figure 8d.3
Skin biopsy, hematoxylin and eosin stain revealing the presence of the amastigotes of *Trypanosoma cruzi* at the dermal-epidermal junction. Note the bar-like kinetoplast adjacent to the protozoan nucleus.

PCR of the patient's serum, as well as skin scrapings taken from the lesion (performed by the Division of Parasitic Diseases branch of the Centers for Disease Control and Prevention), confirmed the diagnosis of *T. cruzi*. Peripheral blood smears did not show evidence of trypomastigotes, but serology for *T.cruzi* was positive. Reevaluation of the explanted heart pathology did not reveal amastigotes within the cardiac tissue. The patient was treated with benznidazole, and after 60 days of therapy the skin lesion had largely resolved (Figure **8d.4**). Subsequent monthly monitoring with *T. cruzi* PCR testing has been negative for further reactivation.



Figure 8d.4
Physical examination after treatment with benznidazole.

**Case 8d Discussion: Chagas Disease**

## Epidemiology and Parasitology

*T. cruzi*, the causative pathogen of Chagas' disease, is a protozoan flagellate of the family Trypanosomatidae, order Kinetoplastida. The motile trypomastigote form has a single flagellum originating near the kinetoplast, which is a DNA-containing structure located in the parasite's single, complex mitochondrion. The flagellum is enveloped in an undulating membrane and runs parallel to long axis of the organism, extending beyond the body as a free, threadlike structure. *T. cruzi* is a zoonosis that has been isolated in a large number of natural reservoir hosts, including over 150 species of wild and domestic mammals.[1]

*T. cruzi* is transmitted by the *Triatoma infestans*, also known as "the kissing bug" (Figure **8d.5**), which acquires the parasite when it takes a blood meal from an infected animal. The infected insect then takes another blood meal from an uninfected host, and during the feeding process the vector defecates near the wound, excreting infective trypomastigotes. The infective trypomastigotes enter the new host's bloodstream through the bite wound or an exposed mucosal surface, and establish acute infection (Figure **8d.6**).[2] While the vast majority of cases of Chagas' disease are transmitted in this manner, there have been reports of acquisition via oral ingestion of infected food, blood transfusion, solid organ transplantation, and congenital routes.[3] Much of the blood supply in the United States is screened for antibodies to *T. cruzi,* and screening in many endemic countries is compulsory.[4] Vertical transmission from infected mother to fetus can occur as well.[2]

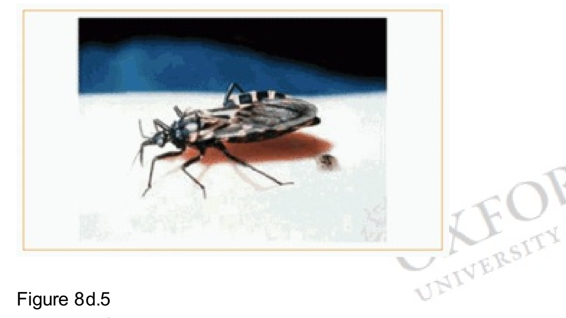




Figure 8d.5
Example of a triatomine bug.

Source: Centers for Disease Control and Prevention.

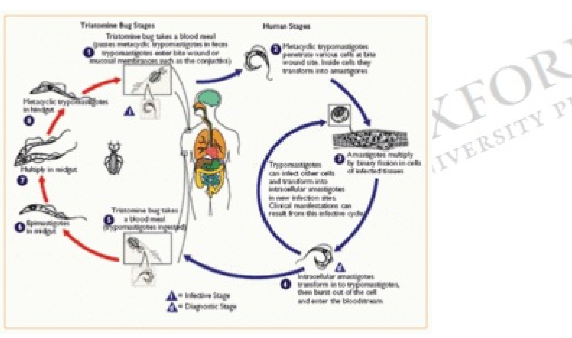






Figure 8d.6
Lifecycle of *Trypanosoma cruzi*.

Source: Centers for Disease Control and Prevention. http://www.dpd.cdc.gov/dpdx



It is estimated that 8 to 9 million people are currently infected with 40,000 incident cases of vector-borne Chagas' disease occurring every year.

Approximately 20,000 persons die every year from Chagas' disease, and most of the disease burden occurs in Latin America where the insect vectors of *T. Cruzi* are native.[5] Chagas' disease is primarily a public health problem among poor persons who live in rural areas.[1] Humans enter the cycle of transmission when undeveloped land is opened for cultivation in areas where *Triatoma infestans* is prevalent. With their habitat and those of their typical mammalian prey violated, the vectors take up residence in the settler's homes, which are frequently primitive and constructed from thatched roofs, mud walls, and stone, which contain numerous niches for the insects to live and thrive. The insects become domiciliary and begin to prey on the resident humans and livestock in the community. Approximately 100,000 persons in the United States are infected with *T. Cruzi*,[6] the vast majority of whom acquired their infections in endemic countries. *Triatoma infestans* is found in the United States, but documented vector-borne cases of Chagas' disease are rare.[2]

Reactivation of Chagas' disease can occur in patients who become immunosuppressed for a variety of reasons including HIV and solid organ transplantation. This issue is particularly germane in patients who undergo heart transplantation for cardiomyopathy caused by chronic *T. cruzi* infection. While post-transplant reactivation of *T. cruzi* infection occurs in approximately one-fourth of patients who undergo heart transplantation for Chagas' disease.[7] The associated mortality is low and can be treated with appropriate antiparasitic therapy.[8]

Most new vector-borne infections occur in children younger than 10 years old.[1] In a study of selected patients, the case fatality rate for untreated acute Chagas' disease was 12%,[1] but such a high rate likely reflects the fact that only seriously ill patients come to medical attention. The case fatality rate for all new infections is probably less than 1%.

## Clinical Manifestations

Acute Chagas' disease usually occurs during childhood in endemic areas, and frequently goes unrecognized because of the mild and nonspecific nature of the symptoms in most patients. Symptoms appear at least a week after infection with the appearance of a chagoma, a characteristic area of erythema, swelling, and induration at the site of entry accompanied by local lymph node involvement. This can be followed by fever, malaise, anorexia, edema of the face and lower extremities, generalized lymphadenopathy, and hepatosplenomegaly. Meningoencephalitis is a rare but serious complication with a poor prognosis. Severe myocarditis resulting in heart failure is uncommon, but can result in death in a small proportion of patients. In untreated patients symptoms gradually improve over weeks to months, eventually resulting in spontaneous resolution of symptoms. The patient subsequently enters the indeterminate or chronic phase of Chagas' disease, characterized by asymptomatic, sub-patent parasitemia, and antibodies to a variety of *T. cruzi* antigens.[1]

Approximately 10% to 30% of persons with chronic *T. cruzi* infections will develop symptomatic Chagas' disease years after resolution of the acute infection, with the heart, esophagus, and colon being the organs most frequently affected. Cardiomyopathy develops insidiously, usually affecting the right ventricle first, but often causing disease in the left ventricle as well. Destruction of the cardiac conduction system results in arrhythmias, a frequent cause of death. Thromboembolism to the systemic and pulmonary vasculature is a frequent complication of severe disease. Symptoms of megaesophagus are similar to those of idiopathic achalasia, and include weight loss, cachexia, dysphagia, odynophasia, chest pain, cough, regurgitation of undigested food, and aspiration pneumonitis. Megacolon is characterized by severe, chronic constipation and abdominal pain. Patients with advanced disease may go weeks between bowel movements, occasionally resulting in obstruction, perforation, volvulus, and death. The symptoms of recrudescent *T. cruzi* infection, which can include fever, myocarditis, and skin lesions (often containing a large number of parasites), can be more severe than those of acute infection in immunocompetent hosts.[1]

## Diagnosis

In acute infection, the level of parasitemia is high, allowing the diagnosis of *T. Cruzi* infection via detection of motile trypomastigotes in a peripheral blood smear or buffy coat. The level of parasitemia will decrease after 90 days, regardless of treatment, making this method of detection unlikely to prove useful in patients with chronic disease. Amastigotes can be found in cutaneous lesions as well, particularly in immunocompromised patients with reactivated disease. Confirmation of chronic Chagas' disease is based on serological methods.[6] PCR techniques are very sensitive in acute disease, although their performance in chronic disease is variable. PCR is becoming an important tool in monitoring patients with Chagas' associated cardiomyopathy who have undergone cardiac transplantation; it frequently detects parasitic reactivation more reliably than traditional microscopic techniques.[9]

## Treatment

There are currently two drugs used in the treatment of Chagas' disease: nifurtimox and benznidazole. Nifurtimox has been shown to be effective in reducing the duration of illness and mortality associated with acute and congenital infection with *T. cruzi*; however, it is associated with a variety of side effects and has a parasitologic cure rate of 70%. The duration of treatment is usually 90 days with nifurtimox, but 60 days with benznidazole. Both agents have a similar efficacy, but benznidazole has fewer medication interactions, a more favorable side-effect profile, and shorter duration of treatment, so it has emerged as the drug of choice.[6] Treatment should be offered to all infants with congenital *T. cruzi* infection, persons with acute or recrudescent disease, and chronically infected children 18 years of age or younger.[6]

Antiparasitic treatment of adults with indeterminate or chronic Chagas' disease is controversial and still being evaluated,[1] though some experts recommend treatment in the absence of advanced Chagas' disease-associated cardiomyopathy.[6] Treatment is mainly supportive for patients with gastrointestinal or cardiac manifestations of chronic Chagas' disease. As noted above, cardiac transplantation is a viable option for patients with severe cardiomyopathy. In one study performed in Brazil, patients who underwent cardiac transplantation because of Chagas' disease associated cardiomyopathy had a better 12 year survival when compared to patients with ischemic or idiopathic cardiomyopathy.[8]

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## Diffuse Colitis and Pseudomembranes

**Chapter:** Diffuse Colitis and Pseudomembranes
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0041

### Case Presentation

A 73-year-old man with multiple medical problems, including diabetes mellitus, COPD, and congestive heart failure, was admitted to the hospital from a long-term care facility with an ankle fracture that resulted from a fall. He underwent open reduction and internal fixation of his ankle fracture, and received cefazolin for perioperative prophylaxis.

On his fourth hospital day, the patient's roommate was diagnosed with *C. difficile* during work-up of diarrhea that began 3 days earlier. Two days later, the patient developed fever, abdominal pain, and altered mental status. The following day, he was found to be hypotensive with persistent abdominal pain and fever. He received fluid resuscitation and was treated empirically with metronidazole. The hypotension resolved, but diarrhea and abdominal pain persisted. A CT scan demonstrated diffuse colitis, and endoscopy revealed colonic pseudomembranes (Figures **9a.1** and **9a.2**).





Figure 9a.1 CT
scan abdomen, axial view showing diffuse bowel wall thickening consistent with colitis.

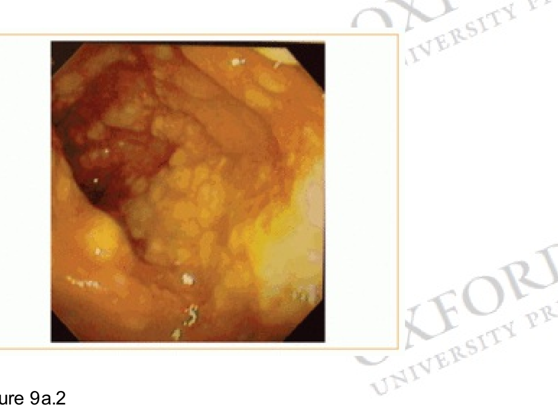




Figure 9a.2
Colonoscopy showing diffuse pseudomembranes.

Over the following days, the patient had progressive leukocytosis, reaching a maximum of 45,000 WBC per $mm^3$. On the eleventh hospital day, the patient developed recurrent hypotension, and orally administered vancomycin was added to his treatment regimen. The following day, vasopressors were initiated for refractory hypotension, and a surgery consult was obtained (Figures **9a.3** and **9a.4**). Later that day, the patient was taken to the OR for partial colectomy. In the recovery room, the patient remained critically

ill with lactic acidosis, elevated liver enzymes, and hypotension. His course was further complicated by ARDS and multiorgan failure. The patient died on hospital day 13.





Figure 9a.3
Resected large intestine with diffuse pseudomembranes and bowel wall edema.

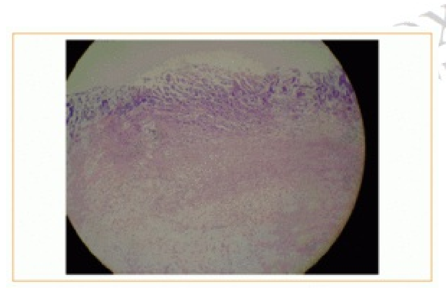


Figure 9a.4
Pathologic section of colon with pseudomembrane, hematoxylin and eosin stain, showing extensive neutrophilic infiltrate.



**Case 9a Discussion: *Clostridium difficile* Colitis**

## Epidemiology and Clinical Presentation

The clinical manifestations associated with CDI range from a mild diarrheal illness to more significant diarrhea with abdominal pain and systemic symptoms, life-threatening pseudomembranous colitis, toxic megacolon, bowel perforation, and death. In addition to these adverse clinical outcomes, patients with CDI also frequently experience prolonged hospitalization and increased healthcare costs.[1,2]

During the past decade, there has been an increase in the reported incidence of CDI in the United States, Canada, and Europe. During the same time period, increases in the frequency of disease recurrence and severe disease have also been reported. These changes in the epidemiology of CDI are temporally associated with the emergence of a previously uncommon strain of *C. difficile*, known as the BI or NAP1 strain.[3, 4]

Although acquisition of *C. difficile* can occur in the community, healthcare settings are associated with the greatest risk of acquisition of, and infection with, *C. difficile*. *C. difficile* frequently contaminates the skin of persons with CDI, as well as surfaces (e.g., bed rails, bedside tables, toilets, sinks) and equipment (e.g., IV poles, blood pressure cuffs) in hospital rooms. Healthcare workers may also play a substantial role in *C. difficile* transmission. Studies have shown that *C. difficile* frequently contaminates the hands or gloves of healthcare workers after providing care to patients with CDI.[5]

A number of host-associated and healthcare-associated factors contribute to the establishment of colonization, and subsequent progression to symptomatic disease, following exposure to *C. difficile*. The major risk factor for CDI is receipt of antimicrobial therapy. Although clindamycin, penicillins, and cephalosporins have historically been most commonly associated with CDI, other classes of antimicrobial agents, including the fluoroquinolones, have been well established as risk factors for CDI. Gastric acid suppressants, such as proton pump inhibitors, have also been associated with CDI in some studies.[3]

A number of host-level factors have also been associated with CDI. These include the presence of certain medical conditions (e.g., chronic renal failure, malignancy, inflammatory bowel disease), malnutrition, severity of illness, and older age.

The humoral immune system also appears to play a role in CDI. Development of serum IgG antibodies against toxin A appears to be associated with a reduced risk of progression to symptomatic disease following colonization, and of recurrence of disease following an initial episode of CDI.[3,2]

## Diagnosis

There are several diagnostic tests that can be useful in confirming a diagnosis of CDI. The most widely used diagnostic test is an enzyme immunoassay (EIA) for *C. difficile* toxin. These assays are somewhat less sensitive than cell-culture-based cytotoxicity assays and stool cultures for toxigenic *C. difficile*, but these more sensitive tests do not provide results as rapidly as EIA-based testing, and require laboratory resources and expertise that are not available in all healthcare facilities. The EIA for glutamate dehydrogenase (GDH) antigen is more sensitive than the EIA for toxins A and B, and has a rapid turnaround time. However, it is relatively nonspecific, and positive tests must be confirmed with a more specific test. Recently, PCR-based testing has become commercially available for use in the diagnosis of CDI. The sensitivity of PCR-based testing has been shown to exceed that of the EIA tests that detect *C. difficile* toxins.[2]

## Treatment

If possible, the antimicrobial therapy associated with the development of CDI should be discontinued. In some instances, this may be the only intervention necessary. However, many patients will require specific treatment of CDI. Orally administered vancomycin remains the only FDA-approved drug for the treatment of CDI. Metronidazole, however, has been the agent most commonly recommended for treatment of mild to moderate disease, due to its lower cost and concerns regarding the potential for selection of vancomycin-resistant organisms, such as *Enterococcus*, with use of vancomycin. Metronidazole also has the advantage of allowing intravenous administration in patients with ileus, or who are otherwise unable to take oral medications. Vancomycin is recommended, however, for patients with severe CDI.[1]

Several alternative antimicrobial agents, including nitazoxanide, ramoplanin, and rifamycins, have been studied for use in the management of CDI. Although some of these agents may offer benefit to some persons with CDI, none appear to provide major advantages over currently available agents, and none have received FDA approval for treatment of CDI. In addition, several non-antimicrobial agents, including toxin-binding agents (e.g., cholestyramine, tolevamer), probiotics (e.g., *Saccharomyces boulardii*), and anti toxin A monoclonal antibodies have been evaluated or are being evaluated for use in combination with standard therapy for CDI.[1]

Approximately 20% of patients with CDI will experience at least one recurrence of the disease. First recurrences can typically be treated using the same approach used for treatment of the primary episode. For patients with multiple recurrences of CDI, or CDI that is not responsive to standard treatments, additional interventions may include higher doses of orally administered vancomycin (250–500 mg every 6 hours), intracolonic administration of vancomycin, intravenous immune globulin, and administration of donor stool. The use of tapering doses of vancomycin has been suggested for treatment of patients with multiple recurrences of CDI.[1]

Finally, some patients with fulminant CDI may benefit from surgical intervention. Factors that have been associated with benefit from colectomy include older age, non-immunocompromised status, WBC count ⟩20,000 cells per $mm^3$, and serum lactate between 2.2 and 4.9 mmol/L.[1] Others have found that a requirement for vasopressors and the presence of mental status changes prior to surgery are associated with mortality following colectomy. This suggests that once multisystem organ failure has developed, the opportunity for benefit from surgical intervention may have been lost. Thus, early surgical consultation should be considered in patients with severe CDI.[1]

## Prevention

Preventive measures attempt to modify factors associated with either exposure to *C. difficile* or the development of symptomatic disease following exposure. Although antibiotic exposure cannot be completely avoided in many patients, judicious use of antimicrobial agents (e.g., appropriate spectrum and duration of treatment) may minimize the risk introduced during necessary courses of therapy. The necessity of other agents that may be associated with CDI, such as proton pump inhibitors, should also be routinely evaluated.[5]

Healthcare-associated exposure to *C. difficile* is perhaps the risk factor for which there is the greatest opportunity for intervention. Interventions that can minimize or prevent contamination of the environment, and the hands and clothing of healthcare workers, such as environmental disinfection, proper hand hygiene, and use of contact precautions, are key components of a *C. difficile* transmission prevention program.[5]

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## Abdominal Pain, Fever, and Weight Loss in a Patient with Crohn's Disease

**Chapter:** Abdominal Pain, Fever, and Weight Loss in a Patient with Crohn's Disease
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Presentation and Case History

A 17-year-old man with Crohn's disease presented with fevers, right lower quadrant abdominal pain, and a 25-pound weight loss over several months. He had been diagnosed with Crohn's disease 6 weeks prior to admission, and had been managed with oral mesalamine and prednisone (20mg daily). His recent exacerbation of abdominal pain was also accompanied by night sweats, right shoulder pain, constipation, and nonbloody emesis.

On physical examination, he was febrile (38.6°C) and had tenderness and guarding of the right lower quadrant of the abdomen. Laboratory studies were significant for leukocytosis (15 x$10^3$ WBC/μl, 90 % neutrophils) and hyperbilirubinemia (total bilirubin 2.3 mg/dl, direct bilirubin 0.5 mg/dl), but otherwise normal liver enzymes (alkaline phosphatase 127 UI/L, alanine aminotransferase 38 UI/L, and aspartate aminotransferase 22 UI/L).

Computerized tomography (CT) of the abdomen showed two adjacent low density lesions in the periphery of the right lobe of the liver, measuring 4.7 cm and 4.4 cm in greatest diameter, consistent with abscesses (Figure **9b.1**). Additionally, there were severe inflammatory changes in the right lower quadrant involving the cecum and terminal ileum consistent with a phlegmon or early abscess.



Figure 9b.1 CT
abdomen, axial view showed two large liver abscesses.

Percutaneous drainage of one of the liver abscesses yielded 30 ml of bloody purulent fluid, and drain was left in place for several days. The direct Gram stain revealed many white blood cells, and moderate Gram-positive cocci in pairs and long chains (Figure **9b.2**), and a pure culture of *Gemella morbillorum* was isolated from the liver aspirate. The patient also underwent surgical resection of the terminal ileum, which was diffusely diseased and associated with abscess;pathologic examination revealed typical findings of Crohn's inflammation and evidence of healed perforation. He was treated with ceftriaxone and metronidazole to complete 6 weeks of total antibiotic therapy, and subsequent imaging revealed resolving hepatic abscesses.

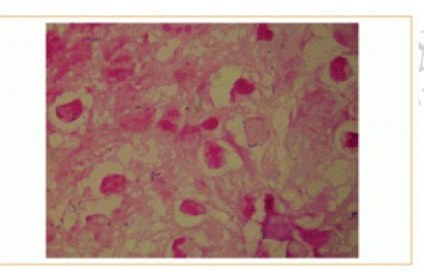




Figure 9b.2
Liver aspirate Gram stain with many white blood cells and moderate Gram positive cocci in pairs and long chains.

**Case 9b Discussion: *Gemella morbillorum* Liver Abscess**

## Clinical Features and Diagnosis

The liver is the most common organ for visceral abscesses, and there are several pathophysiological mechanisms that may lead to liver abscess formation. Hematogenous seeding, direct extension by contiguity, local spread via portal vein, indirect (from a biliary source), hepatic destruction, penetrating trauma, previous surgery or interventional endoscopy, may all lead to formation of pyogenic abscesses. Patients with Crohn's disease tend to have portal bacteremia and, in some cases, pylephlebitis. In some cases, no direct cause is found, but most pyogenic liver abscesses derive from a biliary source.[1]

Once infected, patients may present with constitutional symptoms such as fatigue, fever, weight loss, or anorexia, or can develop nausea, emesis, right upper quadrant pain, diffuse abdominal discomfort, pleuritic chest pain, jaundice, cough, or right shoulder pain. If there are multiple abscesses, shock may be the initial presentation. Common laboratory find-ings include leukocytosis with a left shift, elevated alkaline phosphatase, and slightly elevated transaminases and bilirubin. Blood cultures are positive in 32%–60% of patients. Diagnosis is confirmed with ultra-sound or CT. When found on imagining, pyogenic liver abscesses must be distinguished from other mass lesions such as amebic hepatic abscess, benign and malignant tumors, cystic lesions (including echinococcal cysts), hemangiomas, focal nodular hyperplasia, soft tissue tumors, and inflammatory pseudotumors.[2]

Pyogenic hepatic abscesses are polymicrobial in 11%–65% of cases and monomicrobial in 21%–69% of cases, with anaerobic bacteria growing in 15% to 45% of the culture specimens.[2] The majority of abscesses are caused by enteric flora (particularly Gramnegative bacilli), but anaerobes should be suspected in all polymicrobial abscesses, as they are notoriously difficult to recover in culture. The most frequently isolated organisms are: *Escherichia coli, Klebsiella*, *Proteus*, *Enterococcus, Bacteroides* and *Streptococcus spp.*[2]

*Gemella morbillorum* is a rare cause of liver abscess, especially in patients with Crohn's diseases. *G. morbillorum* is a nonmotile, catalase-negative, facultative anaerobic Grampositive coccus that occurs singly, in pairs, or in chains.[3] It was once considered to be a member of the viridians group of streptococci that are normal human commensals in the lumen of the gastrointestinal tract, but further biochemical analysis resulted in its classification under a separate genus. Fungi are a rare cause of hepatic abscess that occurs more commonly in immunocompromised hosts; *Candida* is the most frequently isolated pathogen, followed by *Aspergillus* species.[4]

In the past, *E. coli* was uniformly the most commonly isolated pathogen in liver abscesses; however, the incidence of *Klebsiella pneumoniae* liver abscesses is increasing, especially in patients with diabetes and of Asian descent. In Taiwan, and in North American cities with large Asian population, such as San Diego, *Klebsiella pneumoniae* has become the most common cause of liver abscess. These patients are found to have positive blood cultures in 95% of cases, with a high incidence of endorgan seeding including eye, lung, pleura, meninges, epidural space, brain, inner ear, spleen, skin, bone, and soft tissue. Metastatic complications occur in 10% to 16% of cases, but endophthalmitis has a greater incidence of 6% to 61%. Diabetic patients are at increased risk for embolic complications with *K. pneumoniae.*[5]

*Entamoeba histolytica* is a protozoan parasite that infects the colon but may also cause hepatic, pulmonary, or brain abscess. Typically, patients with amebic liver abscess present more acutely than those with pyogenic abscess, though similar symptoms of right upper quadrant pain, fever, rigors, chills, and hepatomegaly are reported. Amebiasis is transmitted by ingestion of the cysts in focally contaminated water or food, and occurs more frequently in tropical and subtropical countries, or in returned travelers from endemic regions. Trophozoites

invade the wall of the colon and reach the liver via the portal circulation. Two percent of patients may present with concomitant diarrhea, and some patients may report bloody diarrhea weeks prior to presentation, but the majority of patients do not report preceding symptoms.

In many cases, amebiasis cannot be distinguished from pyogenic liver abscess by clinical presentation or imaging. Stool studies will detect *E. histolytica* in less than 30% of cases, and while serology has a high sensitivity and specificity, it cannot distinguish acute infection from prior exposure in patients from endemic areas. Liver abscess aspiration is generally of low diagnostic value in cases of presumptive amebic abscess. It is rare to find trophozoites in aspirated fluid, as they are typically on the periphery of the abscess and not in the necrotic center. The reddish-brown aspirate is classically described as "anchovy paste" because of the appearance of liquefied necrotic hepatic tissue.[6]

## Treatment

Systemic antibiotics are the mainstay of treatment for liver abscess, and are targeted to the organism's susceptibility.[7] Antibiotics alone may be insufficient to manage large abscesses, due to large bacterial load, inactivation of antibiotics, and ineffective medium for bacterial elimination within the abscess.[7] The initial antibiotic regimen may include a beta-lactam/beta-lactamase inhibitor (ampicillin-sulbactam 3 g IV q6h, piperacillin/tazobactam 3.375 g IV q6h, ticarcillin-clavulanate 3.1 g IV q4h) or a third-generation cephalosporin (ceftriaxone 1g IV q24h) plus metronidazole (500 mg IV q8h). Alternatives for patients with beta-lactam allergies include fluoroquinolones (ciprofloxacin 400 mg IV q12h, levofloxacin 500 mg IV q24h) plus metronidazole (500 mg IV q8h) or carbapenems (imipenem 500 mg IV q6h, meropenem 1g IV q8h, ertapenem 1 g IV q24h). Antibiotic choices should be informed by culture data, but if multiple pathogens are recovered, anaerobes should be assumed to be present. Two to three weeks of intravenous therapy is generally followed by oral antibiotics for a total of 4–6 weeks of treatment. For *K. pneumoniae*, the therapy of choice is a combination of an extended spectrum beta-lactam and a second- or third-generation cephalosporin, with or without an aminoglycoside.[5]

Most pyogenic hepatic abscesses require drainage. Percutaneous drainage is often used as first-line treatment unless urgent surgery is indicated for peritonitis or sepsis, the abscess is large and multiloculated, or there is concomitant biliary or intraabdominal pathology.[7] If multiple abscesses are present, drainage of the largest abscess may be adequate, as the smaller ones may resolve with antibiotics. Despite advances in treatment, mortality in pyogenic liver abscesses is high; Lee et al.[8] (2001), reported a mortality of 6%.

Amebic abscess generally do not require drainage unless they are large and at risk for rupture. For *E. histolytica*, metronidazole 500–750 mg thrice daily orally for 7–10 days is the treatment of choice; alternatives are tinidazole or chloroquine. After the course of metronidazole, patients are treated with an oral luminal amebicide: iodoquinol 650 mg thrice daily for 20 days, paromomycin 25 to 35 mg/kg daily in three divided doses for 7–10 days.[6]

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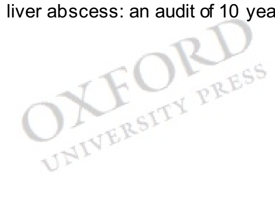
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# Fevers and Chills after Travel to India

**Chapter:** Fevers and Chills after Travel to India
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 24-year-old software programmer from India presented with fevers and chills 6 days after returning from a 3-month trip to India. His symptoms began during his flight back to the United States, and were accompanied by sweats, fatigue, arthralgias, headache, and neck pain. He denied cough, abdominal pain, diarrhea, or urinary symptoms. While in India, he did not take malaria prophylaxis or apply insect repellants, and he reported having consumed tap water while there.

On physical examination, he was febrile (39.2° Celsius) and had mild diffuse abdominal pain on deep palpation, but the remainder of his physical examination was unremarkable. His laboratory studies were notable for mildly elevated liver enzymes (ALT 140 IU/L, ALT 160, IU/L, total bilirubin 2.3 mg/dl, lactate dehydrogenase 720 U/L), but normal white blood cell count (8.1 $\times 10^3$ cells/μl) and platelets (446 $\times 10^3$ cells/μl). Peripheral blood smear for parasites was negative and cerebrospinal fluid analysis was normal (glucose 66 mg/dl, protein 45 mg/dl, 1 white blood cell/μl). The patient was treated with intravenous ceftriaxone, and three sets of initial blood cultures grew ampicillin-susceptible *Salmonella typhi* within 24 hours (Figures **9c.1** and **9c.2**). The patient was switched to ampicillin, continued to improve over the course of several days, and was discharged home on oral amoxicillin.

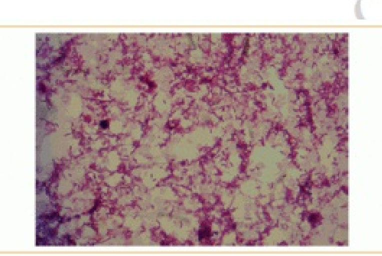




Figure 9c.1
Gram stain from blood cultures with Gram-negative bacilli.





Figure 9c.2
MacConkey media with colonies of a non-lactose fermenting organism later identified as *Salmonella typhi*.

### Case 9c Discussion: Typhoid Fever

*Salmonella enterica* serotype Typhi causes the systemic illness known as typhoid fever, which is endemic in Central and South America, Africa, the Middle East, and Asia.[1]

Infection is transmitted from person to person via fecal–oral spread, in contaminated food or water. The incubation period between ingestion and clinical illness ranges from 3 to 60 days and depends on the inoculum of ingested bacteria. Patients typically present with vague symptoms of fever, headache, flu-like symptoms, nausea, abdominal discomfort, and anorexia. Bacteremia is marked by fever and malaise, and in some cases a relative bradycardia (pulse–temperature dissociation) may be present. Other electro-cardiogram findings that may be observed (particularly in children) include heart block or Wenkebach phenomenon. Rose spots, blanching erythematous maculopapular lesions about 0.5 cm in diameter, may be seen in up to 30% of cases, but may not be visible in darker-skinned patients.[2]

Complications can occur in 10%–15% of patients and include gastrointestinal perforation or hemorrhage, hepatitis, subclinical cholecystitis, heart block, myocarditis, encephalopathy, meningitis, delirium, pneumonia, anemia, disseminated intravascular coagulation, and rarely, shock.[3] Gastrointestinal perforation results from rapid enlargement of lymphoid tissue in the terminal ileum, as the bacteria replicates intracellularly within tissue macrophages. Mother-to-child transmission is rare but has been reported. Relapse is an important complication, which occurs in 5%–10% of patients and is usually defined as recurrence of fever, with or without bacteremia, 2–3 weeks after resolution of the symptoms. Relapses are generally not as severe as the original attack, and blood culture isolates generally exhibit the same antimicrobial susceptibility pattern as the isolate cultured during the initial episode. A small percentage of patients eventually go on to become chronic carriers, excreting the bacteria in stool for up to one year.[2,4]

The gold standard of diagnosis of typhoid fever is a positive blood culture; however, this requires a large volume of blood to be cultured initially (15 ml) in order to increase the sensitivity to 60%–80%. Culture of bone marrow is more sensitive (80%–95% sensitivity) but much less feasible in many resource-limited settings. On blood agar, the organism typically produces nonhemolytic, smooth white colonies, and on MacConkey agar, they produce lactose nonfermenting smooth colonies with a gunmetalgrey appearance. Stool specimens may be cultured for *S. typhi* in acutely ill patients, but are positive in only 30% of patients; nonetheless, they are useful in evaluating possible typhoid carriers.[1,2]

Other non-culture methods of diagnosis include the Felix-Widal test, and newer rapid serological tests such as the Typhidot. The Felix-Widal test measures agglutinating antibody levels against salmonella type O and H antigens. The test has moderate sensitivity and specificity, and can have a false negative rate of up to 30%. In addition, in areas of low endemicity, levels of these antibodies may be high without active disease. The dot enzyme immunoassay (Typhidot) was developed in Malaysia for the detection of IgM and IgG antibodies against a specific *S. typhi* antigen. It takes three hours to perform and has a 95% sensitivity rate, as well as high negative and positive predictive values.[2,4]

Uncomplicated typhoid fever may be managed with oral antibiotics, but resistance to antimicrobials has been an emerging problem. The introduction of chloramphenicol after WWII transformed the disease into a treatable infection that no longer claimed the lives of millions worldwide. Later antibiotics such as ampicillin and trimethoprim/sulfamethoxazole were also found to be effective, but in the last decade, emerging multidrug resistance to these antibiotics has occurred.[1,5] Fluoroquinolones were subsequently accepted to be an optimal treatment for typhoid strains resistant to beta lactam antibiotics, but many parts of Asia now report increasing nalidixic acid-resistant strains. Resistance to nalidixic acid predicts clinical relapse in patients treated with ciprofloxacin even when their isolates appear to be susceptible to ciprofloxacin in vitro.[6] Third-generation cephalosporins and macrolides have been found to be efficacious in treating typhoid fever.[5] Randomized trials have compared macrolides to fluoroquinolones, as well as macrolides to ceftriaxone, with comparable rates of cure and relapse.[6]

Prevention of typhoid fever for travelers to endemic areas includes both vaccination and proper sanitation. Drinking water should be boiled or bottled, and food should be thoroughly cooked before ingestion. Early vaccines, including the killed whole-cell vaccine, had a propensity to cause local swelling and systemic side effects in up to 50% of recipients and are now rarely used. The Ty21a live oral attenuated bacterial vaccine is available in capsule or liquid form, and has been shown to provide individual and herd immunity. It is well tolerated and approved for use in adults and children over 5 years of age, and the duration of protection is estimated to be 3–5 years. The parenteral typhoid Vibased vaccine is most used in travelers to endemic areas, as it harbors relatively few side effects and may be administered in adults and younger children over 2 years of age. A single intramuscular dose confers immunity for 2–3 years.[2,4]

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## Enlarging Liver Cysts in a Woman from Uzbekistan

**Chapter:** Enlarging Liver Cysts in a Woman from Uzbekistan
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 58-year-old woman from rural Uzbekistan was diagnosed with hydatid cysts while in her home country. While there, she had also been given a trial of albendazole, but discontinued the medication due to severe nausea, swelling, and pruritus. She had undergone one previous liver resection in her home country, and subsequently had an injection/resection procedure in New York. Several years later, she again presented with increasing right upper quadrant abdominal pain. She was also having fevers (38.5 Celsius) and had lost approximately 10 pounds over the preceding 3 months due to early satiety. Computed

tomography scanning revealed a large multiloculated cyst that was 11.5cm by 7.4 cm in size (Figure **9d.1**).

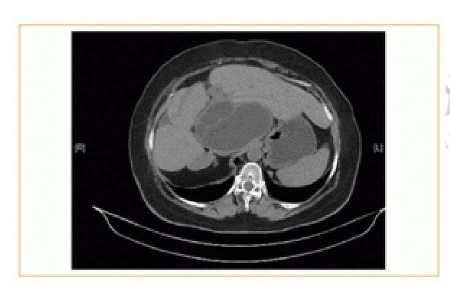




Figure 9d.1 CT
abdomen, axial view showing a large multiloculated hepatic cyst, 11.5cm by 7.4 cm.

*Echinococcus granulosus* IgG antibodies were positive and the patient was noted to have a slight eosinophilia (9%). The swelling she had previously experienced when taking albendazole was thought most likely to be secondary to exposure to parasite antigens, due to leakage of the cyst contents. She was treated again with albendazole and praziquantel, and underwent the PAIR procedure (percutaneous aspiration, installation, and reaspiration). This procedure allowed for the aspiration of cyst contents, installation of hypertonic saline (to kill the remaining parasites in case they are spilled), and reaspiration of the main cyst. The contents of the cyst revealed hooklets of the larval form of the parasite, *Echinococcus granulosus* (Figure **9d.2**). The patient's course was complicated by albendazole-induced alopecia and mild hepatitis, but these side effects reversed upon discontinuation of the medication.





Figure 9d.2
Microscopic examination of cyst contents, showing protoscolex with rings of hooklets.



### Case 9d Discussion: Hydatid Cysts from *Echinococcus granulosus*

## Clinical Presentation and Diagnosis

Hydatid cysts are caused by the zoonotic cestode, *Echinococcus granulosus*. Humans become intermediate hosts in this tapeworm's natural lifecycle between dogs and sheep when they inadvertently consume the eggs of the parasite excreted in dog feces (Figure **9d.3**). The dissemination of the larval form of the organism most commonly causes large fluid-filled cysts in the liver, but these can be found in any organ, including the lungs and the brain.[1,2] The disease is most common in rural societies in Africa, the Middle East, South America, and Southern Europe, in which humans are in close contact with sheep and infected dogs. Another species of *Echinococcus* (*E. multilocularis*) is associated with alveolar cyst disease, and is found in more temperate regions of Europe and North America.[2]

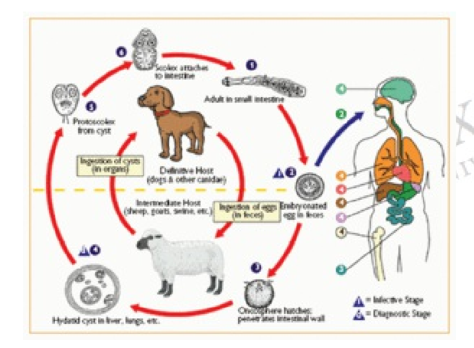



Figure 9d.3
Life cycle of *Echinococcus granulosus*. Source: Centers for Disease Control and Prevention. http://www.dpd.cdc.gov/dpdx/HTML/Echinococcosis.htm

The clinical presentation of hydatid cyst disease is often related to the space-occupying nature of the large (10–20 cm) larval cysts. Patients with pulmonarycysts may present with vomica, a salty tasting fluid that is the sign of a ruptured cyst. Cyst rupture may also lead to severe allergic responses, as parasitic antigens are released into bronchial or abdominal spaces. Cyst rupture is particularly problematic as daughter cysts are formed by the individual parasites within each cyst. Superinfection of cysts by bacteria can lead to the formation of pyogenic abscesses.[2] Diagnosis is often established based on the radiologic appearance (ultrasonography, computed tomography, and magnetic resonance imaging) and confirmed with serologic assays. Serum enzyme-linked immunoassay (ELISA) and Western blot have reported sensitivities of 80%–100% and 88%–96% specificity for he-patic disease, but are less sensitive for hydatid disease involving other sites.[3] Examination of aspirated fluid or resected cysts may reveal the presence of "hydatid sand"—microscopic protoscolices, which often have visible hooklets (see Figure **9d.2**).[3]

## Management

Surgical resection of the cysts had for many years been the treatment of choice for hydatid cyst. These resections can be complicated by spillage of the cyst contents into the abdomen or thorax. Anaphylactoid responses to parasite antigens and further dissemination of cysts are risks of this approach. The PAIR procedure (percutaneous aspiration installation and reaspiration) is designed to remove enough of the cyst fluid so that antiparasitic agents (such as hypertonic saline or 95% ethanol) may be infused to minimize the risk of dissemination the event of spillage of the cyst contents.[2,3] Albendazole or mebendazole are systemic cysticidal agents that are sometimes used in conjunction with mechanical drainage procedures, especially in cases in which complete surgical resection is impossible.[4] Albendazole at doses of 400mg orally twice daily is better absorbed than mebendazole, and may be given over the course of several months for patients with inoperable hydatid cyst disease.[3]

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A-65 Year-Old Heart Transplant Recipient with Abdominal Pain and Altered Mental Status

**Chapter:** A-65 Year-Old Heart Transplant Recipient with Abdominal Pain and Altered Mental Status
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0045

### Case Presentation

A 65-year-old man from the Dominican Republic was admitted with a 2-day history of fever, rigors, abdominal pain, and confusion. The patient had a history of diabetes mellitus, hypertension, and ischemic cardiomyopathy. Four months prior to admission, he underwent an uncomplicated orthotopic heart transplant. He had no prior history of rejection, and he was maintained on tacrolimus, mycophenolate mofetil, and prednisone. He worked as a building superintendant and had not traveled back to the Dominican Republic in over 30 years.

The patient was agitated and febrile to 102.7° F with an otherwise unremarkable physical examination. His laboratory results were significant for hyponatremia (sodium 125 meq/l), mild renal insufficiency, (1.5 mg/dl), and hyperglycemia (156 mg/dl). His peripheral white blood cell count was normal (5.8 x$10^3$/µl) without a leukocytosis or eosinophilia. Broad-spectrum antimicrobials were initiated for a possible systemic infection, after blood, sputum, and urine cultures were collected. Initially he defervesced, but 48 hours later he had recurrence of fevers accompanied by watery diarrhea, dyspnea, and a nonproductive cough. He became increasingly tachypneic and hypotensive, and subsequently required ventilator and vasopressor support. A petechial and purpuric rash abruptly developed over the chest and abdomen (Figure **9e.1**). Radiographs of the lungs, which had been unremarkable on admission, now revealed diffuse interstitial infiltrates and bilateral consolidations (Figures **9e.2** and **9e.3**).






Figure 9e.1
Diffuse petechial and purpuric rash on chest and abdomen.

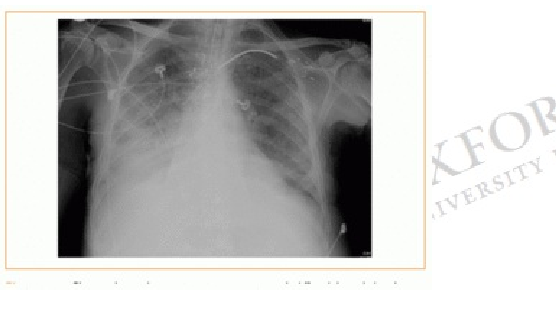





Figure 9e.2
Chest radiograph, anterior posterior view with diffuse bilateral alveo-lar infiltrates and right sided pleural effusion.

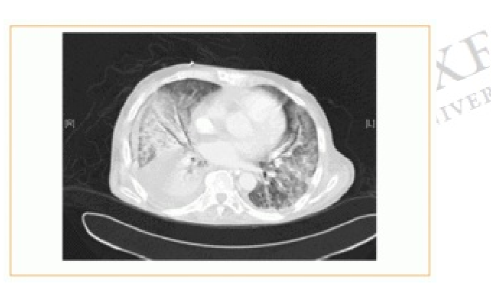
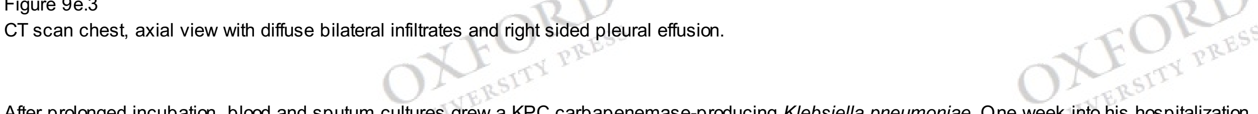


Figure 9e.3
CT scan chest, axial view with diffuse bilateral infiltrates and right sided pleural effusion.



After prolonged incubation, blood and sputum cultures grew a KPC carbapenemase-producing *Klebsiella pneumoniae*. One week into his hospitalization, the patient was not arousable off sedation, and blood cultures continued to grow the same *K. pneumoniae* despite systemic polymyxin B. Non-contrast head CT was unremarkable, and lumbar puncture revealed an elevated protein (953 mg/dl), hypoglycorrhachia (glucose ⟨10mg/dl), and a neutrophilic pleocytosis (650 WBC/ml, 85% polymorphonuclear cells). Cerebrospinal fluid cultures also grew *K. pneumoniae*. The patient was treated with both systemic antimicrobials, and intrathecal polymyxin B and gentamicin. A supervisor in the microbiology laboratory noted serpentine tracks of *K. pneumoniae* on an agar plate of the patient's bronchoalveolar lavage (Figure **9e.4**). She performed wet mounts of the lavage sample, and discovered many motile *Strongyloides stercoralis* filariform larvae (Figure **9e.5**).

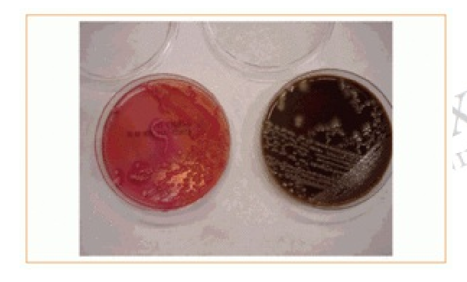


Figure 9e.4
Sputum culture on MacConkey agar and chocolate agar. The colonies of Klebsiella *pneumoniae* where being dragged across the plate in serpiginous tracks.





Figure 9e.5
Wet mount of sputum revealed many motile larvae of *Strongyloides stercoralis*.

Despite administration of ivermectin and thiabendazole via nasogastric tube, and daily ivermectin retention enemas, the patient demonstrated little neurologic recovery. Magnetic resonance imaging revealed a discrete abscess in caudate nucleus, as well as diffuse enhancement of the ventricles (Figure **9e.6**). Due to the overall grave prognosis, palliation was pursued and the patient expired.

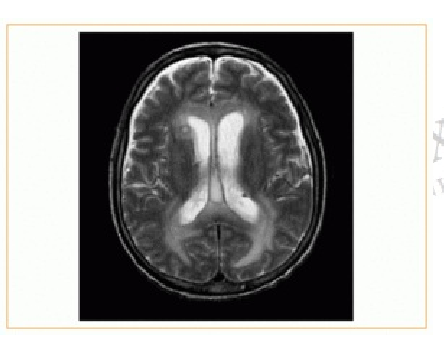




Figure 9e.6
MRI brain, axial view revealed a discrete abscess in the right caudate nucleus as well as diffuse enhancement of the ventricles.

**Case 9e Discussion: *Strongyloides stercoralis***

## Clinical Features and Diagnosis

*Strongyloides stercoralis* is prevalent in tropical and subtropical climates. Areas of endemicity include Central and South America, Asia, Africa, the Caribbean, the southeastern United States, and Mexico. *S. stercoralis* has the ability to autoinfect a single human host and establish a latent infection that can persist asymptomatically for years. Hyperinfection occurs when the autoinfection process accelerates in the setting of immunosuppression, either from underlying medical conditions or medications like corticosteroids or antithymocyte immunoglobulin. *Strongyloides* hyperinfection syndrome (SHS) has been associated with mortality rates of as high as 87% in the immunocompromised host.

Primary strongyloidiasis begins with filariform larvae transcutaneously infecting the human host. These larvae travel through the venous circulation to the lungs, where they penetrate the alveoli. They then travel to the pharynx and are subsequently ingested. Larvae mature into adult worms within the gastrointestinal tract, and eggs are deposited within the intestinal mucosa. The hatched rhabditiform larvae are either excreted into stool or develop into filariform larvae within the intestinal tract. Autoinfection occurs when these filariform larvae migrate through the bowel wall, or through the perianal skin, into the venous circulation (Figure **9e.7**). A creeping purpuric rash in the perianal or pelvic area, "larva currens," is often suggestive of autoinfection. In the setting of endogenous or exogenous immunosuppression, the autoinfection cycle is accelerated. Massive larval migration through the lungs causes respiratory symptoms that may be as mild as cough and wheezing, to as life-threatening as acute respiratory distress syndrome and respiratory failure. Gastrointestinal symptoms range from diarrhea and abdominal pain to paralytic ileus and intestinal obstruction. The high volume parasitic migration can also lead to the development of diffuse larva currens. Biopsy of these lesions can reveal migrating larvae. Bacteremias with enteric flora are often suggestive of SHS in the appropriate host. SHS should always be considered in the differential when treating patients with Gram-negative meningitis. Visualization of larvae on biopsy or on ova, and parasite examination of stool or sputum, is diagnostic. Tracking of bacterial colonies on solid culture media is also suggestive.

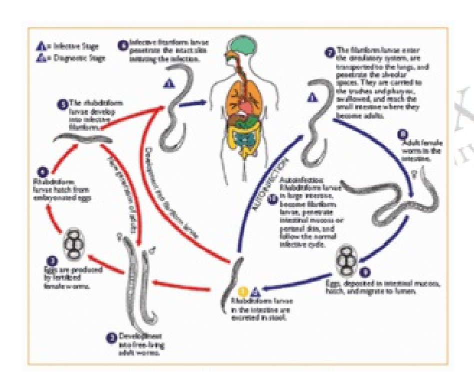


Figure 9e.7



Lifecycle of *Strongyloides stercoralis*. Source: Centers for Disease Control and Prevention http://www.dpd.cdc.gov/dpdx.

In solid organ transplantation, most reported cases of SHS are the result of reactivation of latent infection in the setting of intensified immunosuppression.[1] Most reports describe patients presenting within the first 3 months after transplantation. In retrospect, many case patients had evidence of occult infection prior to transplantation, including unexplained intermittent eosinophilia, chronic gastrointestinal symptoms, or a history of another intestinal parasitic infection.[2] Primary *Strongyloides* infection in areas of endemicity and donor-derived primary infection are rare, but have been described.[3]

Often the diagnosis of SHS in the solid organ transplant recipient is serendipitous, as in the described case. The critical nature of Gramnegative bacteremia, respiratory failure, or altered mental status can delay the diagnosis. Hallmarks of parasitic infections like diarrhea or eosinophilia are usually absent in the setting of SHS. A thorough history, including a detailed travel history and review of any augmentation or changes in immunosuppressive medications, can be helpful.

## Management

The ideal treatment of SHS is not well established. Single dose ivermectin is the treatment of choice in immunocompetent patients with intestinal strongyloidiasis. Treatment duration for SHS using thiabendazole monotherapy ranges from 5 to 14 days. More aggressive regimens for SHS employ thiabendazole or albendazole and ivermectin for variable durations. Many patients require multiple courses of therapy because of persistent parasitosis. It has been suggested that survivors of SHS should be treated monthly for at least 6 months. Reactivation can occur in transplant recipients even after initial treatment. These patients may benefit from indefinite therapy, but studies to support this practice are lacking.

A challenge in the treatment of SHS is that patients often suffer from paralytic ileus or intestinal obstruction, preventing both administration and absorption of oral agents. No accepted parenteral therapy exists, but employment of alternative treatment modalities such as subcutaneous and rectal formulations of ivermectin have been described.[4,5]

## Pretransplant Evaluation

This case highlights the importance of developing strategies to prevent *Strongyloides* infections in transplant recipients. Donors and recipients who have resided in endemic areas should be screened for latent strongyloidiasis prior to transplantation. Those with a history of other helminthic infections, unexplained eosinophilia, or unexplained gastrointestinal complaints should also be screened. Serology may be less sensitive in relatively immunocompromised patients, and diagnostic yield may be greater with concomitant examination of stool for ova and parasites. Transplant candidates with evidence of *Strongyloides* infection should be treated with either thiabendazole 25 mg/kg twice daily for three days, or ivermectin 200 mcg/kg once daily for two days with documented negative stool ova and parasite exams prior to transplantation. At the time of transplantation, with the initiation of high-dose immunosuppression, treatment should be reinitiated. Family members and pets should also be screened and treated as potential sources of reinfection post-transplant.

Pretransplant screening of the deceased donor prior to organ procurement is not practical. Targeted serologic screening for *Strongyloides* in donors from endemic areas may provide useful information for the physicians caring for the recipients of organs from an untreated cadaveric donor with latent *Strongyloides*. Although formal studies are lacking, preemptive treatment in these recipients may prevent disease.

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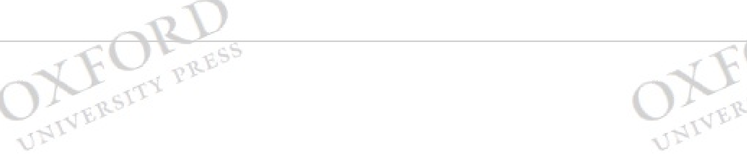







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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

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## A Liver Transplant Recipient with Fever and Abdominal Pain

**Chapter:** A Liver Transplant Recipient with Fever and Abdominal Pain
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 41-year-old man with hepatitis C cirrhosis and hepatocellular carcinoma who underwent liver transplantation 6 months earlier, presented to the emergency room with abdominal pain, nausea, and vomiting for 2 weeks. In addition to his abdominal pain, he had multiple episodes of loose watery stools for several days, and on the day of presentation he had chills and fever at home to 101° Fahrenheit. Two months prior to presentation, his immunosuppression had been increased because he had developed acute elevation of liver enzymes, and liver biopsy showed moderate acute cellular rejection.

His past medical history also included diabetes and hypertension. His immunosuppressive medications included cyclosporine 150 mg twice daily, prednisone 5 mg daily, and mycophenolate mofetil 1000 mg twice daily (recently increased from 500 mg twice daily). Prophylactic valganciclovir 900 mg daily and trimethoprim-sulfamethoxazole had been discontinued per protocol 3 months prior to presentation, after having completed a 3-month course posttransplant. Of note, he was CMVseronegative at the time of transplant, and had received the liver from a CMV seropositive donor. He lived with his wife and young daughter, and denied any pets or recent travel.

On physical examination, he was febrile to 38.5° Celsius and had a blood pressure of 134/74 mm/Hg with heart rate of 72 beats per minute. He appeared uncomfortable and was vomiting. His physical examination was also significant for bilateral crackles at the lung bases, and diffuse abdominal tenderness to palpation. Laboratory examination was nota-ble for leukopenia (3.9 x$10^3$WBC/μl, 82% neutrophils), thrombocytopenia (60 x$10^3$platelets/μl), elevated BUN (31), creatinine (1.4 from a baseline of 1.1), and liver enzymes (ALT 267 U/L, AST 78 U/L). The liver enzymes had improved from 2 months prior when, in the setting of acute rejection, they were 350 U/L and 320 U/L respectively; the total bilirubin was 1.8 with a direct bilirubin of 1.4.

A chest radiograph revealed bilateral interstitial infiltrates (Figure **9f.1**) and subsequent chest CT showed diffuse ground-glass opacities and nodular lung infiltrates with small bilateral pleural effusions (Figure **9f.2**). Over the next several days, he developed worsening shortness of breath, progressive hypoxia and confusion, and was intubated and transferred to the medical intensive care unit.





Figure 9f.1
Chest radiograph, posterior anterior view showing bilateral interstitial infiltrates.







Figure 9f.2 CT
chest, axial view with diffuse ground glass opacities and nodular lung infiltrates with small bilateral pleural effusions.

The admission cytomegalovirus (CMV) PCR was ⟩100,000 copies/ml, and the patient was treated initially with intravenous ganciclovir and subsequently with foscarnet, for the possibility of ganciclovir-resistant CMV. Flexible sigmoidoscopy revealed scattered sigmoid ulcers, and typical CMV inclusions were found on colonic biopsy and confirmed with immunohistochemical staining (Figures **9f.3** and **9f.4**). Transbronchial biopsy did not confirm CMV pneumonitis, but other infections were excluded, and this was thought to be the most likely cause of the pulmonary findings. Over the course of his hospitalization he received broad-spectrum antimicrobials in addition to foscarnet, ganciclovir (after ganciclovir resistance was excluded), and cytomegalovirus intravenous immune globulin (Cytogam). His CMV PCR was undetectable 4 weeks after admission, but his course was complicated by prolonged respiratory and renal failure. After a 2-month hospitalization, he developed nosocomial sepsis with multidrug resistant *Acinetobacter baumannii,* and died despite full ventilatory and pressor support.

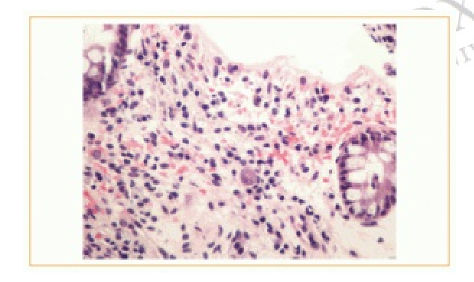


Figure 9f.3
Colon biopsy, hematoxylin and eosin stain showing characteristic viral inclusions of cytomegalovirus. Image courtesy of Alexandros D. Polydorides.

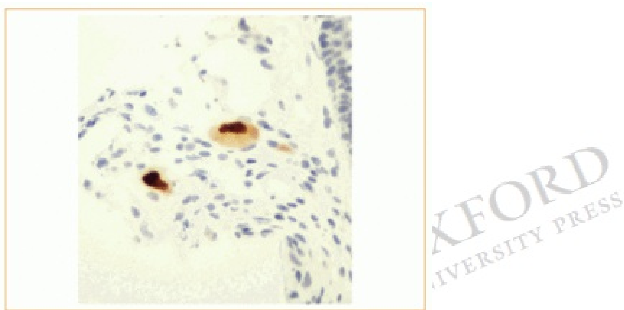


Figure 9f.4
Colon biopsy, immunohistochemical stain specific for Cytomegalovirus antigen. Image courtesy of Alexandros D. Polydorides.

**Case 9f Discussion: Cytomegalovirus Colitis**

CMV is a herpesvirus that infects the majority of adults by the third decade of life, and is a major cause of morbidity and mortality in solid organ transplant patients. As with all herpesviruses, CMV establishes latency in different cell types and can reactivate to cause secondary infection in the setting of immunosuppression in solid organ transplant recipients.

In the absence of a preventive strategy, 30%–75% of transplant recipients will develop CMV disease.[1] As in the case described above, CMV donor positive/recipient negative (D+R-) patients are at the highest risk for CMV disease because of the lack of previous CMV-specific immunity. These patients have a 44%–65% risk of developing CMV disease without the use of antiviral prophylaxis, and a 12%–30% risk with antiviral prophylaxis.[2] CMV seropositive recipients are also at risk for reactivation, but the risk is lower than for D+R-patients. Although D+R-status remains the most important risk factor, other risk factors play a role as well. These include the use of highly immunosuppressive medications post-transplant, including antithymocyte globulin, muromonab-CD3 (OKT3), and increased doses of mycophenolate mofetil or corticosteroids after an episode of graft rejection. Other risk factors include coinfection with other viruses including HHV-6 or HHV-7, or allograft rejection itself.

The terminology surrounding CMV infection can be confusing. The term *CMV infection* refers to the presence of CMV virus as detected by PCR or antigen testing in body fluid or tissue specimen, but may be asymptomatic. The term *CMV disease* refers to CMV infection with signs and symptoms such as fever, malaise, and bone marrow suppression (leukopenia and thrombocytopenia).

*Tissue-invasive CMV disease* refers to any organ system affected by CMV, and is usually based on a biopsy for diagnosis.[1]

In solid organ transplant patients, CMV infection can manifest with both direct and indirect effects. Direct effects of CMV in various organ systems include gastrointestinal disease such as colitis, as in the case above, hepatitis, pneumonitis, CNS disease, or retinitis. In addition to direct effects, CMV may have a number of indirect effects. These include an increased risk of acute or chronic allograft rejection, with manifestations such as accelerated coronary atherosclerosis in heart transplant recipients, and bronchiolitis obliterans in lung transplant recipients. In addition, CMV infection has been associated with the development of other opportunistic infections, including viral infections, EBV-

associated post-transplant lymphopro-liferative disease (PTLD), and fungal infections. Through both direct and indirect effects, CMV disease has been independently associated with an increased risk of mortality in solid organ transplant recipients, and therefore prevention plays a vital role in this population.

## Prevention

There are two approaches recommended for the prevention of CMV disease: a preemptive strategy, or universal prophylaxis. With a preemptive strategy, patients are followed closely after transplant for CMV, with polymerase chain reaction (PCR) assays, or markers such as pp65 antigenemia testing. If the assay becomes positive, antiviral therapy is initiated immediately. With a prophylaxis approach, antiviral prophylaxis is administered immediately after transplant for a period of 3–6 months, depending on the type of transplant and transplant center protocols.[3]

Both approaches have been used successfully and are effective at preventing CMV disease. Several meta-analyses have compared the preemptive and prophylaxis approaches, and have shown both strategies to be effective. In the meta-analysis published by Kalil et al, the authors compared 17 randomized controlled trials looking at CMV prevention using either prophylaxis or a preemptive strategy.[4] In this meta-analysis, both approaches showed significant reduction in CMV disease and allograft rejection; however, in patients who received anti-lymphocyte antibody and were D+R-, only prophylaxis showed a reduction in CMV disease. In addition, only the prophylactic approach showed a significant decrease in bacterial and fungal infections, and death.

The preemptive approach has several advantages, despite these shortcomings. This approach minimizes the cost and toxicities associated with the prophylactic antiviral drugs. In addition, it may allow for the development of an early CMV-specific immune response, reducing the risk of late-onset CMV disease, which remains a significant problem after prophy-laxis is discontinued. Lastly, the use of the preemptive approach may lower the risk of the development of CMV resistance to ganciclovir—a phenomenon that has been shown to be associated with prolonged use of antiviral therapy.

The American Society of Transplantation guidelines recommend antiviral prophylaxis in high-risk solid organ transplant recipients. In D+R-patients who receive kidney, liver, pancreas, or heart transplants, ganciclovir or valganciclovir is recommended for 3–6 months. In R+ or R-patients who receive a lung or heart–lung transplant, and in patients who receive anti-lymphocyte antibody or OKT3, prophylaxis is recommended. In R+ patients who receive a kidney, liver, pancreas, or heart transplant, either prophy-laxis or the preemptive monitoring strategy is recommended (please see Table 9f.1).[5] A preventive strategy should be resumed in the setting of acute rejection, particularly in patients treated with corticosteroids or antilymphocyte therapies.

Table 9f.1 Guidelines for Prevention of CMV in SOT Recipients

| Organ/group | Recommendation/Options (see text for dose, evidence rating and special pediatric issues) |
|---|---|
| Kidney, liver, pancreas, heart | Prophylaxis: Valganciclovir, oral ganciclovir, or intravenous ganciclovir (or valacyclovir in kidney) for 3 to 6 months. Some centers add CMV immune globulin for heart transplant. |
| D+/R– | Preemptive therapy an option (see Figure 1). Many authorities prefer to use prophylaxis and reserve preemptive therapy for lower-risk populations (see text). |
| Kidney, liver, pancreas, heart | Valganciclovir, oral ganciclovir, intravenous ganciclovir or valacyclovir (kidney) for 3 months. Some centers add CMV immune globulin for heart transplant *OR* |
| R+ | Pre-emptive therapy an option (See Figure 1). |
| Lung, heart-lung | For D+/R– patients valganciclovir or intravenous ganciclovir for 6 months. Some centres with prolong prophylaxis beyond 6 months. |
| D+/R–, R+ | For R+ patients, valganciclovir, oral ganciclovir or intravenous ganciclovir for 3–6 months. Some centres will add CMV immune globulin especially for D+/R–. |

The above guidelines do not represent an exclusive course of action. Several factors may influence the precise nature and duration of prophylaxis or preemptive therapy.

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Several agents are used for the prevention of CMV, and include either ganciclovir or valganciclovir. Ganciclovir, the first antiviral approved for CMV, is available in both intravenous (IV) formulations and oral formulations, but the oral formulation has limited bioavailability. Valganciclovir, a valyl ester prodrug, enhances absorption and results in systemic drug levels comparable to IV ganciclovir. The role of valganciclovir in prophylaxis was evaluated in a randomized clinical trial in which 364 D+R-SOT recipients received either 900 mg of valganciclovir once daily, or 1000 mg of ganciclovir three times daily.[6] At 12 months, the proportion of patients receiving valganciclovir who developed CMV was similar to those who received oral ganciclovir (17.2% and 18.4%); however, in a subset analysis performed on the 177 liver transplant recipients who participated in this trial, the incidence of CMV disease, including tissueinvasive disease, was higher in the valganciclovir group as opposed to the ganciclovir group (19% vs. 12%). For this reason, valganciclovir never gained FDA approval for prophylaxis against CMV disease in liver transplant patients. Despite these findings, valganciclovir is routinely used in the prevention of CMV disease in liver transplant patients.

Late-onset CMV disease presents a challenge almost exclusively in patients who receive prophylaxis, and typically occurs within the first year. It is associated with D+R- status and higher mortality after transplantation. Newer strategies are needed to monitor these patients once prophylaxis is discontinued. These may include monitoring with CMV PCR, using immunological markers such as conversion of CMV serostatus, or the development of CMV-specific

CD4+ or CD8+ cells, or extending the duration of prophylaxis. Currently, the IMPACT (the Improved Protection Against Cytomegalovirus in Transplant) study is an ongoing randomized, multicenter, placebo-controlled trial designed to look at whether extending prophylaxis in high-risk renal transplant recipients is effective in preventing late-onset CMV disease. Preliminary data at one year shows that in D+R-renal transplant recipients who received 200 days of prophylaxis, there were decreased rates of CMV disease, including tissue-invasive disease, as compared to patients who received 100 days of prophylaxis (16.1% vs. 36.8%).[7]

## Treatment

For treatment of CMV disease, IV ganciclovir is recommended, and oral ganciclovir should not be used because of its poor bioavailability. Oral valganciclovir has also been shown to be effective in the treatment of CMV disease. In 321 solid organ transplant recipients with CMV disease, who were randomized to receive either valganciclovir or IV ganciclovir for treatment for 21 days followed by 4 weeks of step-down therapy, the proportion of patients with viral eradication at 21 days and then 49 days was comparable.[8] Therefore, for selected patients, valganciclovir can be used for the treatment of disease.

Duration of therapy has not been studied in a clinical trial, but induction treatment is generally continued until CMV DNA is no longer detectable in the serum by PCR, and

signs of clinical disease have resolved. The need for maintenance or secondary prophylaxis or post-treatment surveillance remains unsettled.

Ganciclovir-resistant CMV is an emerging clinical problem in solid organ transplant recipients. It should be suspected in patients who do not initially respond to ganciclovir. The mechanism of resistance is related to mutations in either the UL97 or UL54 genes of CMV. CMV D+R-recipients, recipients of pancreas or lung transplants, and those who receive ganciclovir for prolonged periods of immunosuppression are at high risk.[9] Intravenous foscarnet should be considered for these patients or in patients with confirmed ganciclovir-resistant CMV. Because of its nephrotoxicity, foscarnet use requires careful monitoring of renal function and electrolytes.

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## Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management

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# Methicillin-Susceptible *Staphylococccus aureus* (MSSA) Pyelonephritis

**Chapter:** Methicillin-Susceptible *Staphylococccus aureus* (MSSA) Pyelonephritis
**Author(s):** Daniel Caplivski and W. Michael Scheld
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## Case Presentation

A 58-year-old male with history of hypertension and dyslipidemia presented with a 9-day history of lower back pain leading to decreased mobility in his left leg. He was evaluated at a local emergency department, and a CT scan of the spine at the time was negative for any lesions. He was discharged home with a prescription of cyclobenzaprine, but returned with severe lower back pain with numbness and weakness in the left lower extremity. On admission to our institution, he also reported fever and night sweats, but denied any other symptoms. He denied any history of substance abuse or recent travel.

Physical examination on admission was significant for fever and decreased left lower extremity muscle strength to 2/5. His laboratory examinations were notable for leukocytosis ($32.7 \times 10^3$ WBC/μl) and mild renal insufficiency (BUN 33 mg/dl, creatinine 1.5 mg/dl). Urinalysis showed 1–5RBC, 10–20WBC, many bacteria, and urine culture grew ) 100,000 CFU/ml of methicillin susceptible *Staphylococcus aureus* (MSSA); blood cultures were sterile (Figure **10a.1**).



Figure 10a.1
Axial (A) and sagittal (B) non-contrast abdominal CT demonstrates perinephric fat stranding (arrows) along with increased size of the right kidney, consistent with right sided pyelonephritis (representative image courtesy of Joshua Dowell).

CT of the abdomen revealed pyelonephritis of the left kidney, and MRI of the spine revealed discitis/osteomyelitis at L2-L3 with a small epidural abscess. Epidural aspirate also grew MSSA. A transthoracic echocardiogram did not reveal any evidence of endocarditis and the patient made a full recovery following 6 weeks of intravenous nafcillin.

### Case 10a Discussion: *Staphylococcus aureus* Pyelonephritis

Urinary tract infections (UTI) are among the most common complications associated with the use of indwelling urinary catheters (IDUC). *Staphylococcus aureus* ascending UTI is uncommon; bacteriuria in this case may be secondary to bacteremia. The association of *S. aureus* bacteriuria (SABU) with *S. aureus* bacteremia (SAB) has been well described in the literature.[1,2,3]

*S. aureus* is recognized to cause UTI or colonization in patients with IDUC, recent instrumentation, surgery, or urinary tract obstruction. Several studies have shown that the presence of *S. aureus* in the urine is not just an incidental colonization, especially in patients without IDUC.[1,4,5] *Staphylococcus aureus* bacteriuria is associated with a high risk of future invasive infection, and can be an early surrogate of *Staphylococcus aureus* bacteremia.[4,5] *Staphylococcus aureus* bacteriuria in a recent study appears not to be, as previously reported,[6] associated with more SAB fatality.[5]

Current risk factors associated with concomitant SABU-SAB include: the presence of an underlying urinary tract abnormality, urinary tract surgery, or instrumentation. Choi et al.[5] found vertebral osteomyelitis to be a frequent focus of infection associated with concurrent SABU-SAB. Community-onset MSSA SAB vs nosocomial cases appear to be more associated with concurrent SABU-SAB.[5]

Because of the severity of complications that may be related to staphylococcal bacteremia, SABU should not be considered as a simple colonization. Investigation for possible occult deep foci of staphylococcal infection should be performed with blood cultures, imaging studies, and transthoracic and/or transesophageal echocardiography.

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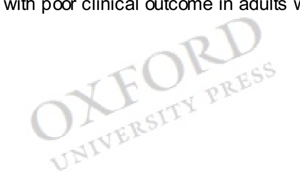
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## A 19-Year-Old Stem Cell Transplant Recipient with Hematuria

**Chapter:** A 19-Year-Old Stem Cell Transplant Recipient with Hematuria
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 19-year-old man from China with severe transfusion-dependent aplastic anemia underwent cord transplantation from an incompletely matched donor. His conditioning regimen included antithymocyte globulin, cyclophosphamide, and total body irradiation. On day 47 after transplant, his bone marrow had engrafted, but he presented to the transplant clinic with dysuria and hematuria for 2 weeks. He reported passing blood and clots in the urine, but he had no fevers, chills, or back pain. His immunosuppressive medications included cyclosporine and mycophenolate mofetil.

On admission, he was afebrile and with no flank pain or suprapubic tenderness. His laboratory values were significant for anemia (hemoglobin 8.4 g/dl) and thrombocytopenia (platelets 124,000 cells per microliter) but normal leukocyte count (WBC 5800 cells per microliter) and creatinine (0.7 mg/dl). Abdominal ultrasound did not show any hydronephrosis or renal calculi, but the bladder wall had a lobular contour, and scattered internal echogenic material was seen within the lumen (Figure **10b.1**). Urine cultures were negative, but urine cytology revealed atypical urothelial cells with ground-glass intranuclear inclusion bodies (Figure **10b.2**). Urine and blood PCR testing for BK virus were positive, and serum CMV PCR was negative. Cyclosporine was discontinued and intravenous fluids were administered, and the hematuria eventually resolved within 2 days.



Figure 10b.1
Abdominal ultrasound showing a lobular contour to the bladder wall and scattered intraluminal echogenic material.

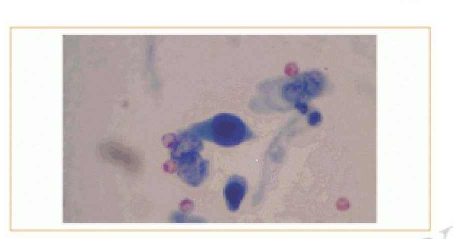





Figure 10b.2
Urine cytology revealed atypical urothelial cells ("decoy cells") with ground-glass intranuclear inclusion bodies.

#### Case 10b Discussion: BK Virus Hemorrhagic Cystitis

Clinical Presentation and Diagnosis

# A 19-Year-Old Stem Cell Transplant Recipient with Hematuria

BK virus is a member of the polyoma genus of viruses that also includes JC virus, the etiologic agent of progressive multifocal leukoencephalopathy. The polyoma virus genus derives its name from their ability to cause multiple tumors in mice. The individual viruses were named for the initials of the patients from whom they were first isolated. These viruses are extremely common among healthy adults, but can cause profound invasive reactivation disease in immunosuppressed patients. In kidney transplant recipients, BK virus causes a post-transplant nephropathy or ureteral stenosis that may lead to graft loss. In stem cell transplant (SCT) recipients, hemorrhagic cystitis is the major manifestation of BK virus disease.

Hemorrhagic cystitis is a clinical syndrome characterized by hematuria, caused by hemorrhagic inflammation of the bladder mucosa. Symptoms may include dysuria, urgency, frequency, and suprapubic pain. Complications include urinary tract obstruction and renal failure when clots are present. Hemorrhagic cystitis may be caused by multiple etiologies, including chemotherapy (e.g. cyclophosphamide) and bladder irradiation early after SCT, but once engraftment occurs, viral infections such adenovirus and BK virus are more common etiologies.[1]

The diagnosis of BK nephropathy or hemorrhagic cystitis is usually supported in kidney transplant or SCT recipients with PCR testing of urine or blood. BK viruria is found in up to 20% of asymptomatic individuals, but viremia is uncommon outside of the setting of immunosuppression. Detection of BK virus DNA in the blood is more useful in evaluating patients for BK nephropathy than for those with hemorrhagic cystitis, in whom blood PCR testing is rarely positive.[2] Renal biopsy or urine cytology are also used to establish the diagnosis of BK nephropathy or hemorrhagic cystitis. Renal biopsy may reveal tubular epithelium cells with large intranuclear inclusions. Decoy cells are atypical-appearing urothelial cells, with a large basophilic intranuclear inclusion indicative of viral infection, but are not specific to BK virus, as JC and adenovirus infections can produce similar findings.[2,3]

## Management

The principle intervention required for BK virus nephropathy or ureteral stenosis is reduction in the degree of immunosuppression. Symptomatic management of hemorrhagic cystitis with bladder irrigation, forced hydration, analgesia, and blood transfusions, is generally adequate. Anecdotal reports of success with the use of cidofovir and quinolone antibiotics are problematic because of the lack of control groups, and the fact that these patients also were treated with reduced immunosuppression.[3]

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## Multidrug-Resistant Organisms

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### Case Presentation

A 56-year-old man with hepatitis C cirrhosis underwent orthotopic liver transplantation for decompensated liver failure. Prior to transplant, he required hemodialysis for worsening renal failure from hepatorenal syndrome, as well as ureteral stent placement for obstructive nephrolithiasis of his right kidney. His immunosuppressant medications included prednisone, tacrolimus, and mycophenolate mofetil.

Ten days after liver transplantation, he was no longer requiring hemodialysis but he developed fevers (39°C), chills, and lethargy. On physical examination, he was slow to answer questions and had a flat affect. He denied any urinary complaints; however, he was having palpitations and was found to be in rapid atrial fibrillation. His laboratory results were significant for leukocytosis ($12 \times 10^3$ WBC per μl) and renal insufficiency that was slowly improving (BUN 61 mg/dl, creatinine 3.1 mg/dl). His urinalysis revealed numerous white blood cells, and both blood and urine cultures were positive for Gram-negative bacilli (Figure **10c.1**). This organism was confirmed to be a KPC-producing *Klebsiella pneumoniae* resistant to all antibiotics except tigecycline (Figure **10c.2**). The patient was treated with tigecycline, but the bacteremia persisted until the ureteral stent was removed and the patient underwent ureteroscopy, laser lithotripsy, and stent exchange.

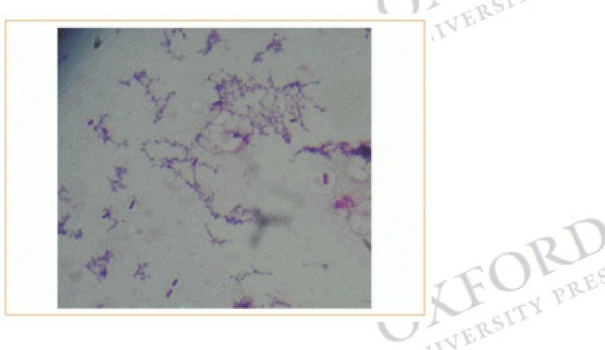


Figure 10c.1
Blood culture Gram stain showing Gram-negative bacilli. The area of clearing around several of the organisms is caused by the polysaccharide capsule.

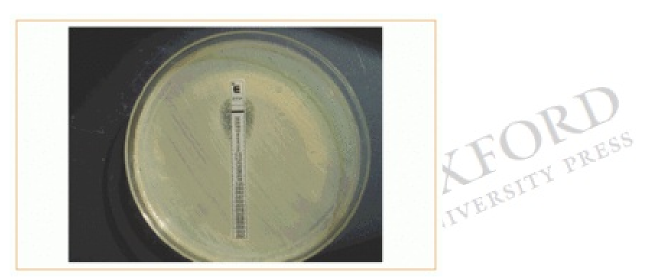




Figure 10c.2
E-test showing ertapenem-resistant *Klebsiella pneumoniae*.

**Case 10c Discussion: KPC-producing *Klebsiella pneumoniae***

## Epidemiology and Microbiology

Carbapenem resistance among Enterobacteriaceae was first recognized in the early 1990s. Isolation of these bacteria remained sporadic for the better part of that decade. In recent years, however, healthcare-associated infections with carbapenem-resistant Gram-negative bacilli, specifically *Klebsiella pneumoniae,* are being reported at an alarming rate.[1] In 2007, the United States' Centers for Disease Control and Prevention noted that 8% of all *K. pneumoniae* responsible for healthcare-associated infections were carbapenem-resistant, compared with less than 1% in 2000. Thirty-three states have reported clinical isolation of carbapenem-resistant Enterobacteriaceae with a concentration of cases in the northeast United States.[2]

Carbapenem resistance in Enterobacteriaceae results from one or a combination of the following mechanisms: hyperproduction of AmpC β-lactamases, loss of outer membrane porins, drug efflux, or carbapenemase production. In the United States, Greece, and Israel, carbapenem-resistance in Enterobacteriaceae is attributed primarily to plasmid-mediated expression of a Class A serine carbapenemase—*Klebsiella pneumoniae* carbapenemase (KPC). These enzymes are capable of efficiently hydrolyzing carbapenems, as well as other β-lactam antibiotics like penicillins, cephalosporins, and the monobactam aztreonam, rendering these entire classes of agents inactive. KPC production has been identified in many Enterobacteriaceae, and in both *Acinetobacter* and *Pseudomonas* species. *K. pneumoniae* remains the most common species found to harbor these enzymes. Nine KPC subtypes (KPC-2 through KPC-10) have been reported, with the majority of analyzed isolates expressing either KPC-2 or KPC-3.

Microbiologic identification of these organisms is difficult, and may lead to delays in therapeutic management and implementation of appropriate infection control measures. KPC-mediated carbapenem resistance can go completely unrecognized in laboratories that rely solely on automated identification and susceptibility testing. Recommendations have been made to perform additional testing (e.g., the Modified Hodge Test or PCR) on isolates demonstrating discordant carbapenem susceptibilities, or elevated MICs to any one of the carbapenems. Ertapenem has been identified as the most sensitive agent to detect Enterobacteriaceae-producing KPCs (KPC-E) in vitro.[3]

Early observational reports aiming to identify risk factors for the acquisition of KPC-E, specifically carbapenem-resistant *K. pneumoniae*, suggest that patients at risk are critically ill and have exposures to multiple antibiotic classes. In most of these studies, clinical isolation of carbapenem-resistant Enterobacteriaceae was associated with in-hospital mortality. A single center study from New York City demonstrated that 48% of patients with invasive carbapenem-resistant *K. pneumoniae* infections did not survive their index hospitalization. In this study, infection was independently associated with recent transplantation, length of stay, and exposure to cephalosporins and carbapenems.[4] Clinical isolation of KPC-E has also been described throughout Europe, South America, the Caribbean, and Asia. Most reported cases are sporadic and have rarely been associated with exposure to healthcare systems in areas of endemicity the United States, Israel, and Greece.

## Management

There is a paucity of agents available to treat KPC-E infections. There is in vitro evidence suggesting that some KPC-E are susceptible to aminoglycosides, polymyxins, and the glycylcycline tigecycline. No universal agent to treat these bacteria has been identified.

Polymyxins, both polymyxin B and E (colistin), fell out of favor with the advent of more specific and tolerable antibiotics. The clinical reintroduction of these antimicrobials initially came with the emergence of carbapenem-resistance in *P. aeruginosa* and *A. baumannii*. By analogy, clinicians have extended their use to the treatment of KPC-E. Increasing isolation of KPC-E from sites where polymyxins do not reliably penetrate (e.g., lung and cerebrospinal fluid) has become a concern in the treatment of the critically ill patients. Chemical ventriculitis can be a side effect of intrathecal polymyxin therapy, and bronchospasm has been associated with aerosolized drug. Systemic polymyxins are also associated with renal insufficiency and a myriad of neurologic sequelae. Most adverse events have been reversed with the discontinuation of the drug.[5]

Tigecycline, a glycylcycline, is licensed for use in the treatment of skin and soft tissue infections, community-acquired pneumonia, as well as complicated intra-abdominal infections. Tigecycline has demonstrated in vitro activity against many highly drug-resistant bacteria including carbapenem-susceptible ESBL-producing *Escherichia coli* and *K. pneumoniae*. The pharmacodynamics of glycylcylines indicate that they may not achieve appropriate concentrations in the bloodstream or genitourinary system, however, further clinical studies are indicated.[6]

There are a number of case reports and case series recounting the successful treatment of KPC-E with both polymyxins and tigecycline. Many accounts involve employment of an adjunctive therapeutic procedure (e.g., catheter removal, peritoneal lavage, or decortication of an empyema), in addition to systemic antimicrobials. One study suggested that in patients with invasive carbapenem-resistant *K. pneumoniae*, use of an adjunctive procedure to remove a focus of infection was independently associated with survival.[4] Anecdotal successes aside, the true clinical efficacy of these salvage antibiotics remains unclear.

The increasing prevalence of KPC-E is not only a diagnostic and therapeutic challenge, but also presents a significant threat to patient safety. Evolving epidemiology, an awareness of limitations in the clinical microbiology laboratory, and an appreciation of risks for the development of drug resistance should prime practitioners to suspect possible infection with these highly resistant bacteria in appropriate populations. In regard to management, clinicians are to be encouraged to remove possible foci of infection, and to be familiar with susceptibility patterns within their own institutions. Due to the limited antimicrobial options available to treat infections with KPC-E, an increased emphasis should be placed on early and accurate laboratory detection of these carbapenemases, and early implementation of appropriate infection control measures to decrease potential healthcare-associated transmission.

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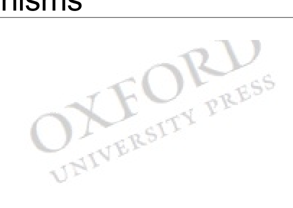
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## An 84-Year-Old Man in Septic Shock

**Chapter:** An 84-Year-Old Man in Septic Shock
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

An 84-year old man with a past medical history significant for atrial fibrillation, congestive heart failure, hypertension, BPH, and spinal stenosis presented to the emergency department with fevers, chills, shortness of breath, and increasing confusion. His medications at home included atenolol, digoxin, furosemide, coumadin, prednisone, and terazosin.

On physical examination, he was febrile (38.7°C) and tachycardic (190 bpm); after receiving diltiazem for atrial fibrillation with rapid ventricular rate, he became hypotensive (70s systolic) and tachypneic (32 bpm) and was admitted to the medical intensive care unit for management of sepsis.

His laboratory examinations were notable for leukocytosis (28 × $10^3$ WBC/μl and acute renal failure (3.9mg/dl). His initial urinalysis showed numerous white blood cells and 4+ bacteria. He was treated with empiric cefepime for management of septic shock. CT of the abdomen revealed an enlarged prostate gland with a 7.6 × 6.4 cm abscess with bubbles of air (Figure **10d.1**). Blood cultures grew *Escherichia coli,* and urine culture grew Group B *Streptococcus* and *Escherichia coli* (Figure **10d.2**). The antibiotic was changed to ampicillin-sulbactam for coverage of a likely mixed infection including anaerobic organisms.



Figure 10d.1
CT abdomen, axial view showing an enlarged prostate gland with a 7.6 × 6.4 cm bilobed shaped complex fluid density structure with bubbles of air.

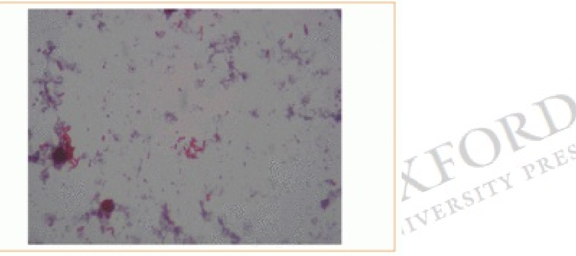




Figure 10d.2
Blood culture Gram stain with Gram-negative bacilli later identified as *Escherichia coli*.

The patient underwent transurethral unroofing of the prostatic abscess; using transrectal ultrasound, a pus collection was identified and drained. Several days later, the patient

underwent definitive transurethral resection of the prostate. He defervesced and his elevated white blood cell count and renal failure resolved. He completed an extended course of oral antibiotics for chronic prostatitis.

**Case 10d Discussion: Prostatic Abscess**

Prostatitis accounts for an estimated two million visits to the primary care physician or urologist yearly. About 8% of visits to urologists and 1% of visits to the primary care doctor are coded with the diagnosis of prostatitis. The term *prostatitis* is used to refer to various complaints relating to the lower urogenital tract and perineum. According to NIH consensus classification guidelines, prostatitis may be classified into four major groups—acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain syndrome, and asymptomatic inflammatory prostatitis. Prostatic abscess, as described in the patient above, is a rare complication of acute or chronic prostatitis.[1]

Patients with acute bacterial prostatitis often present with symptoms of urinary tract infections, dysuria, or urinary frequency. In addition, they may experience obstruction caused by prostatic edema, and associated systemic symptoms including fever, chills, lower abdominal discomfort, and myalgias. On physical examination, rectal examination reveals a tender prostate on palpation. On laboratory examination, there is pyuria and bacteriuria on urinalysis. Urine culture is frequently positive, and Gram-negative organisms predominate with *Escherichia coli* being the most frequently isolated organism. Treatment involves urinary catheter drainage along with 4 weeks of antimicrobial therapy.[2,3]

Unlike acute bacterial prostatitis, chronic prostatitis accounts for the majority of patients presenting with prostatic symptoms, and remains a challenging group to both diagnose and treat. These patients often have recurrent symptomatic infections, despite being asymptomatic in between infections. Traditionally, the gold standard for diagnosis of bacterial prostatitis is the “four-glass test,” and was first described by Meares and Stamey in 1968. This involves obtaining segmented urine cultures of the lower urinary tract to localize infection to the prostate gland (Table 1, from Mandell). Bacterial prostatitis is confirmed by the presence of leukocytes in the expressed prostatic secretions, and bacterial counts in the voided bladder 3 (VB3) sample that greatly exceed the bacterial counts in the voided bladder 1 or 2 sample (VB1 or VB2). Despite being the gold standard, the “four-glass test” is often not carried out in clinical practice because it is considered time-consuming and expensive; therefore, a simpler screen, the pre- and post-massage test (PPMT), has been described. This test involves microbiological evaluation of the urine prior to and after massage of the prostate gland, and was found to have a sensitivity and specificity of 91%.[2]

In chronic prostatitis, a positive bacterial culture is only obtained in about 5% of patients. This group is categorized by the NIH as *chronic bacterial prostatitis,* and diagnosis is characterized by bacterial persistence despite being treated with multiple antimicrobial courses. Microorganisms frequently isolated include Gram-negative rods of the *enterobacteriaceae* or *pseudomonas* family; Gram-positive organisms can be seen in a few cases (most commonly *Enterococcus*). In patients in whom an organism is isolated, antibiotic treatment is recommended for 4–6 weeks. Because penetration into the prostatic secretions is poor, given the barrier between prostatic stroma and the microcirculation, and because of the acidic pH of the prostate, low dose oral antibiotics are recommended for an extended duration. This is done in order to achieve maximal penetration and prevent long-term consequences of untreated prostatitis, including abscesses. Recommended antibiotics include sulfonamides, macrolide, or fluoroquinolones, which have been shown to achieve higher therapeutic levels in prostatic secretions as well as to penetrate bacterial “biofilms” that often form in prostatic ducts and can lead to microabscesses.

Prostatic abscess is a rare entity that is described as a complication of acute or bacterial prostatitis, and may occur in patients not treated or treated inadequately for prostatitis. Patients at risk include those immunocompromised from HIV/AIDS or diabetes, and patients with bladder outlet obstruction or recent urethral manipulation. In the pre-antibiotic era, prostatic abscesses were commonly found in young men in association with gonococcal urethritis. More recently, the pathologic mechanism is thought to be related to either urinary reflux or hematogenous dissemination from a primary focus. In the first, microorganisms isolated include those from the *Enterobacteriaceae* family; in the second, *Staphylococcus aureus* is the most common organism isolated.[4–6]

The signs and symptoms of prostatic abscess are not specific, but are comparable to those of acute prostatitis. On rectal examination, a large boggy prostate is usually felt and, rarely, fluctuance may be detected as well. Delay in treatment can cause bladder or urethra fistulization, or rectal or anal fistulas depending on the location; alternatively rupture of the abscess into the ischiorectal fossa or into the perivesical space is associated with high morbidity and mortality.

More recent imaging modalities such as transrectal ultrasound, CT, and MRI have increased diagnostic reliability preoperatively, and have also influenced therapeutic options. Unroofing of the abscess via transurethral drainage or transurethral radical prostectomy are surgical options for treating the infection, as well as related hypertrophy. Transperineal needle aspiration has also been described as an alternative form of drainage. Transrectal ultrasound guidance may aid in aspiration of the abscess, and can also be used to aid in transperineal drainage.[7]

Patients with chronic prostatitis/chronic pelvic pain syndrome, in which no microorganism is isolated, represent greater than 90% of patients evaluated for prostatitis, and remain the most difficult group to treat. These patients have vague pelvic and perineal symptoms, mainly consisting of urological pain, but also urinary symptoms or sexual dysfunction. The hallmark characteristic of patients in this category is the lack of microbiological evidence revealing bacterial infection of the prostate. Two subtypes are described—inflammatory and noninflammatory. In the inflammatory subtype, formerly termed *nonbacterial prostatitis*, leukocytes may be detected in the urine, prostatic secretions, or semen. In the noninflammatory subtype, formerly known as *prostatodynia*, no inflammatory evidence or leukocytes are seen. Current therapy includes anti-inflammatory therapy and pain management. A trial of initial antimicrobial therapy may be useful in patients with inflammation; however, in patients with prolonged symptoms without inflammation, several studies, including two randomized trials, have shown that antimicrobial therapy in this group is not effective.[1] In one study of Veteran’s Affairs patients, fluoroquinolones were shown to be inappropriately prescribed and overused in patients with chronic pelvic pain syndrome.[8]

Asymptomatic inflammatory prostatitis includes men who are asymptomatic but found to have evidence of prostate inflammation. This may be found in the form of inflammatory infiltrates on pathology after prostate biopsy for elevated PSA, or during removal of benign prostate tissue for treatment of obstruction. Many men may also be diagnosed by semen analysis during evaluation for infertility, and are often treated with an empiric antimicrobial therapy.[1]

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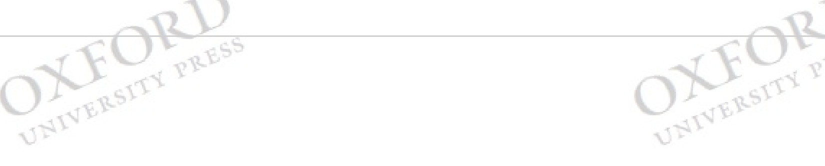
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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 21-Year-Old Man with Recurrent Abscesses

**Chapter:** A 21-Year-Old Man with Recurrent Abscesses
**Author(s):** Daniel Caplivski and W. Michael Scheld
**DOI:** 10.1093/med/9780199735006.003.0051

### Clinical Presentation and History

A 21-year-old man with a diagnosis of Job's syndrome (Hyper-IgE syndrome) was admitted to the hospital with a large right buttock abscess. The patient had a history of recurrent skin abscesses resulting in frequent hospital admissions, as well as an empyema in 2006 that had required surgical drainage. An IgE level performed at an outside hospital in 2004 was markedly elevated at 68,424 (normal ( 180). Cultures from prior drainage procedures were positive for methicillin-susceptible *Staphylococcus aureus* (MSSA), and his most recent admission had been 10 months prior to this presentation, at which time he had bilateral axillary abscesses (Figure **11a.1**).





Figure 11a.1
CT thorax, coronal view showing large complex axillary abscess.

He had been prescribed trimethoprim/sulfamethoxazole for chronic suppression of staphylococcal skin and soft tissue infections in the past, but was nonadherent with this treatment. According to the patient, the current buttock abscess began approximately 3 months prior to presentation, but the patient was living out of state at that time, and had not sought care sooner due to insurance concerns. On physical examination, he appeared older than stated age, with multiple healed acne scars on the face and coarse porous facial skin. He had a broad nose and prominent forehead. He was febrile to 38.6° Celsius but his cardiovascular and pulmonary examinations were unremarkable. The patient had a large abscess on the right buttock, with purulent and foul-smelling drainage.

Computed tomography of the pelvis demonstrated a large multiloculated subcutaneous abscess in the right buttock, extending from the level of the sacral coccyx to the right iliac wing abutting the gluteal muscles, measuring 18 × 13 × 6.5 cm (Figure **11a.2**). The initial white blood cell count was 16,500/µl, with 76% neutrophils, and the patient's other laboratory values were unremarkable. The patient was treated with intravenous vancomycin, and on the day following admission he was taken to the operating room for incision and drainage of the abscess. Gram stain of the pus revealed Gram-positive cocci in clusters engulfed by neutrophils, and culture grew methicillin-resistant *Staphylococcus aureus* (Figure **11a.3**).



Figure 11a.2
CT of the pelvis, axial view showing a large multiloculated subcutaneous abscess in the right buttock, extending from the level of the sacral coccyx to the right iliac wing abutting the gluteal muscles, measuring 18 × 13 × 6.5 cm.

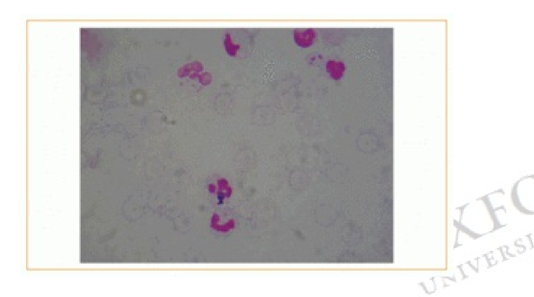
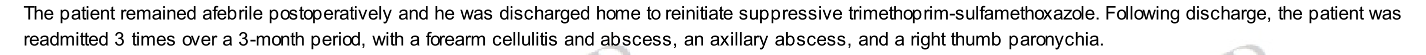


Figure 11a.3
Gram stain of the pus revealed Gram-positive cocci in clusters engulfed by neutrophils.

The patient remained afebrile postoperatively and he was discharged home to reinitiate suppressive trimethoprim-sulfamethoxazole. Following discharge, the patient was readmitted 3 times over a 3-month period, with a forearm cellulitis and abscess, an axillary abscess, and a right thumb paronychia.



**Case 11a Discussion: Methicillin-Resistant *Staphylococcus aureus* Infection**

## Clinical Features and Diagnosis

The hyper-IgE syndrome (HIES), or Job's syndrome, is a rare immunodeficiency disease characterized by elevated levels of IgE, eczema, and recurrent skin and pulmonary infections, first described[1] in the 1960s. The disease was given this name after the biblical character Job, who was covered in boils from head to toe, and was later termed HIES, once the association with elevated IgE levels was discovered. In addition to recurrent skin and pulmonary infections, many patients with the disease share physical characteristics unrelated to the immune defect, including craniofacial abnormalities, hyperextensibility of joints, retained primary teeth, and fractures with only minimal trauma.[1] The typical facial features of Job's syndrome patients include asymmetry, a prominent forehead, and broad nose. A higher rate of vascular abnormalities (such as aneurysms) and non-Hodgkin's lymphoma has also been described in HIES.[1]

Recurrent skin and pulmonary infections begin in early life for patients with hyper-IgE syndrome. Dermatologic findings include moderate to severe eczematous rashes, as well as boils or abscesses. *Staphylococcus aureus* is usually responsible for the abscesses associated with this disease.[1] The other major infectious complication is pneumonia, frequently leading to the development of pneumatoceles, which can become superinfected, requiring thoracotomy and drainage.[2] While the acute pneumonia is often caused by *S. aureus*, *Streptococcus pneumoniae* or *Haemophilus influenza,*[1] these pneumatoceles typically become superinfected with Gram-negative organisms (such as *Pseudomonas*), molds (including *Aspergillus*) and nontuberculous *Mycobacteria*.[1]

Case series have demonstrated significant fluctuation in the IgE levels of patients with Job's syndrome.[2] Notably, the IgE level also does not appear to correlate with infectious or dermatologic complications of the disease. The hyper-IgE syndrome is inherited as an autosomal disorder with incomplete penetrance, but numerous sporadic cases have been reported as well.[1] The disorder has no predilection for a specific race or gender.[1]

Although no unifying mechanism to explain the immunologic and nonimmunologic findings of HIES is as yet understood, the immunologic defect is thought to be due to a mutation in STAT 3.[1] STAT 3 is a cytoplasmic protein involved in signal transduction pathways for many cell types, including multiple cytokines such as IL-6 and IL-10.[1] Recent developments have demonstrated that one major impact of STAT 3 mutation is the impaired production of Th17 cells (CD4 lymphocytes that produce IL-17). These cells are integral in fighting infection through the recruitment of neutrophils and macrophages; this defect is central to the vulnerability of HIES patients to infections with fungi and extracellular bacteria.[1]

## Therapy

There is no treatment for HIES itself; therefore, the management of patients with the disease revolves around the treatment and prevention of recurrent infections. Surgical drainage is essential to the cure of soft tissue abscesses, and antibiotic therapy is often administered adjunctively. Because *S. aureus* is usually the cause of skin and soft tissue infections in this population, antibiotics that target *Staphylococcus* including MRSA are appropriate empiric therapeutic choices. Vancomycin is the standard antibiotic for skin and soft tissue infections due to MRSA, but alternatives include linezolid, daptomycin, and tigecyline.[3]

Despite the fact that there is little data to support therapy aimed at eliminating *S. aureus* colonization, this approach is worthy of consideration in patients with recurrent staphylococcal infections, such as those with Job's syndrome.[4] Preventive strategies include chlorhexidine body washes, mupirocin nasal decolonization, and suppressive antibiotic therapy with anti-staphylococcal agents such as trimethoprim-sulfamethoxazole.

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## A 60-Year-Old Woman with Diabetes Mellitus and Severe Leg Pain

**Chapter:** A 60-Year-Old Woman with Diabetes Mellitus and Severe Leg Pain
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 60-year-old woman with diabetes mellitus, chronic obstructive pulmonary disease, and vulvar cancer presented with 5 days of severe right leg pain and swelling. She had been treated for stage IV vulvar cancer with chemotherapy and local radiation, and had been in remission for 2 years. When she initially presented, her pain was severe enough that it was interfering with her ability to walk.

Upon admission to the hospital, she was febrile (temperature of 38.7), tachycardic (109 beats per minute), hypoxic (88% on ambient air), and hypertensive (144/64). Her physical examination was notable for erythema and swelling of the right lower extremity that extended from her calf to the vulva. There was no numbness, fluctuance, or crepitus noted, but the leg was so exquisitely tender that she was unable to cooperate completely with physical examination. Her initial laboratory values revealed a leukocytosis (14,000 WBC/µl, 67% neutrophils, 26% bands), thrombocytosis (platelets 591,000 per µl), mild anemia (hemoglobin of 11.3 grams/dl), and hyperglycemia (glucose 267 mg/dl). She was treated initially with intravenous ampicillin/sulbactam and vancomycin. Over the course of several hours, her pain became progressively worse, and she required intravenous morphine in order to tolerate the computed tomography scan of her lower extremities (Figures **11b.1 and 11b.2**).

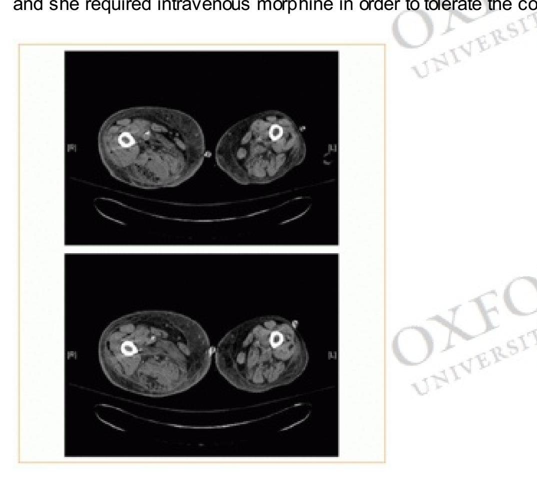




Figure 11b.1 and 11b.2
CT lower extremities, axial view showing multiple rim-enhancing fluid collections within fluid and air.

Computed tomography scanning revealed multiple rim enhancing fluid collections within the right obturator internus, the adductor, gluteal, the vastus, and the biceps femoris muscles. The collections contained fluid and air, and the largest measured 6.5 × 10.7 cm and extended to the knee inferiorly. The patient was emergently taken to the operating room for extensive debridement of the necrotic tissues in her leg. The Gram stain of the debrided tissue revealed Gram-positive cocci in short chains, and cultures of all the debrided material were positive for the beta-hemolytic colonies of *Streptococcus agalactiae* (Group B *Streptococcus*; Figures **11b.3** and **11b.4**).

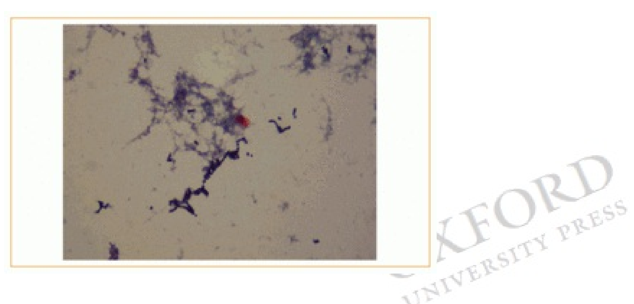




Figure 11b.3
Gram stain of the debrided tissue showing Gram-positive cocci in short chains.





Figure 11b.4
Cultures of all the debrided material showing the beta-hemolytic colonies of *Streptococcus agalactiae* (Group B *Streptococcus*).

The patient would eventually require 12 separate operations for debridement, skin grafts, and colostomy, because of the necrotic tissue that extended to the perineal region. After the first debridement, she was in septic shock and required vasopressors for several days, but she eventually recovered. Her hospitalization lasted 3 months and she was eventually discharged to a rehabilitation facility after several weeks of intravenous antibiotics and surgical debridements.

**Case 11b Discussion: *Streptococcus agalactiae* Necrotizing Fasciitis**

## Microbiology and Epidemiology

Group B *Streptococcus* (GBS) is a facultative, beta-hemolytic, Gram-positive coccus that divides in pairs and chains and grows readily on a variety of growth mediums. Identification of Group B streptococci may be confirmed with detection of Group B–specific cell wall antigen via latex agglutination, though many labs now employ automated biochemical methods. Group B streptococci have the ability to adhere to numerous mucosal and endothelial surfaces, including the vaginal, intestinal, and respiratory epithelium, the endothelium of the blood–brain barrier, and placental membranes. These organisms may cross these barriers paracellularly, and disseminate via translocation from colonized epithelial surfaces to otherwise sterile sites. Group B streptococci possess a polysaccharide capsule that inhibits complement fixation and phagocytosis, and is an important virulence factor.[1]

Group B *Streptococcus* is a frequent colonizer of the rectum and female genital tract, with a colonization rate of approximately 20%. Higher colonization rates are associated with frequent sexual intercourse or multiple sexual partners, African-American race, and lower socioeconomic status. The prevalence of oropharyngeal colonization in adults is about 5%, but approaches 20% in men who have sex with men. The rate of colonization in older, otherwise healthy adults is 20%.[1]

The incidence of invasive Group B streptococcal disease in neonates has decreased since the institution of intrapartum prophylactic antibiotic therapy in pregnant women found to be colonized with Group B streptococci.[2, 3] Among infants younger than 6 days of age, the rate of invasive Group B streptococcus infections decreased from 0.47 per 1000 live births in 1999–2001 to 0.34 per 1000 live births in 2003–2005. The incidence in infants aged 7–89 days and pregnant women was unchanged at 0.34 per 1000 live births and 0.12 per 1000 live births, respectively.[1]

While the incidence of Group B streptococci infection in neonates has decreased, recent studies have shown an increase in the incidence of invasive infections in adults. From 1999 to 2005, the incidence of invasive infections with Group B streptococci increased from 3.4 per 100,000 to 5.0 per 100,000 in persons between the ages of 15 and 64, and from 21.5 per 100,000 to 26.0 per 100,000 in adults greater than 65 years of age; the overall incidence in adults increased from 6.0 per 100,000 in 1999 to 7.9 per 100,000 in 2005.[4]

## Clinical Presentation and Diagnosis

Group B streptococcal infection in neonates is a serious disease, and typically presents with bacteremia/sepsis, meningitis, or pneumonia. In neonates younger than 7 days of age, presenting symptoms typically occur at birth or in the first few hours of life, and include lethargy, poor feeding, abnormal temperature, grunting respirations, pallor, and hypotension. Chest radiography will frequently reveal pulmonary infiltrates, and analysis of CSF will show evidence of meningitis. Maternal complications are frequently associated with higher rates of invasive disease in this age group. Group B streptococcal infection in infants between the ages of 7 and 89 days may present similarly to that in younger infants, but is frequently associated with a variety of focal infections, including osteomyelitis, septic arthritis, and cellulitis. Preterm infants are at a much higher risk for invasive Group B streptococcal infection then those born at term.[1]

Invasive infection in adults is frequently severe and associated with substantial morbidity and mortality. The most frequent clinical syndromes are primary bacteremia without an evident focus, and skin or soft tissue infections, such as cellulitis, infected decubitus ulcer, osteomyelitis, septic arthritis, and wound infection. Less common syndromes include pneumonia, urinary tract infections, meningitis, peritonitis, and endocarditis. Risk factors for invasive infection include older age, HIV infection, the presence of malignant neoplasms, cirrhosis, diabetes, stroke, decubitus ulcer, and neurogenic bladder.[5, 6]

The diagnosis of invasive Group B streptococci infection requires the isolation of the organism from an otherwise sterile site. Group B streptococci grow easily on most growth mediums and can be readily distinguished from other streptococcal species via detection of Group B–specific cell wall antigen (see above).

## Management and Prevention

Group B streptococci are susceptible to penicillin, the cephalosporins, and carbapenems. Penicillin G remains the drug of choice for the vast majority of invasive infections in

adults, though vancomycin can be used in patients with serious allergies to penicillin. Combination therapy with ampicillin and an aminoglycoside is typically used in cases of neonatal bacteremia or meningitis as initial treatment, though treatment can be completed with penicillin G once the diagnosis of invasive infection with Group B streptococci is established and clinical response is documented.[2]

As noted earlier, neonatal infection with group B streptococci can be prevented with appropriate prophylaxis of pregnant women. Lower vaginal and rectal swab screening cultures should be performed at 35 to 37 weeks of gestation for all pregnant women, with the exception of patients with documented Group B streptococcal bacteriuria during the current pregnancy, or with a previous infant with invasive Group B streptococcal disease.[2] Indications for antibiotic prophylaxis are presented in Figure **11b.5**. When culture data is unavailable, prophylaxis is indicated in cases of preterm labor, if amniotic membranes rupture for 18 hours or longer, and if fever is present during labor. Prophylaxis is never indicated for planned cesarean delivery performed in the absence of labor or membrane rupture, regardless of culture status or history of Group B streptococcus infection.[1] Penicillin G is the preferred drug for antibiotic prophylaxis because of its narrow spectrum and documented efficacy; ampicillin should be avoided because of its relatively broad spectrum and subsequent risk of increased antibiotic resistance.

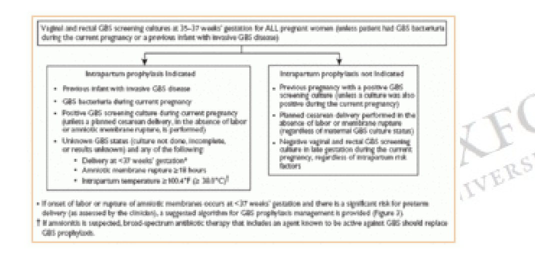





Figure 11b.5
Indications for intrapartum antibiotic prophylaxis to prevent perinatal GBS disease under a universal prenatal screening strategy based on combined vaginal and rectal cultures collected at 35–37 weeks' gestation from all pregnant women. Source: Centers for Disease Control and Prevention. Schrag S, Gorwitz R, Fultz-Butts K et al. Prevention of Perinatal Group B Streptococcal Disease: Revised Guidelines from CDC. *MMWR Recomm Rep*. 2002;51(RR–11):1–77.

Necrotizing fasciitis (NF) is a subcutaneous infection that can be categorized between mixed infections (Type I) and single organism infections (Type II). Type II NF is more typically associated with Group A *Streptococcus,* which produces superantigens that cause nonspecific activation of T-cells and resultant recruitment of massive numbers of neutrophils. The fascial planes provide no anatomic barrier to the spread of infection, and thus NF can progress rapidly over several hours. Clinical presentation can be difficult to distinguish from other causes of extremity pain and swelling, such as cellulitis and deep venous thrombosis. Severe pain, numbness, and discoloration of tissues may be important clues, but a high index of suspicion is required given the rapidly progressive nature of this infection. As with necrotizing fasciitis caused by other organisms, necrotizing fasciitis associated with Group B *Streptococcus* is a medical emergency requiring immediate surgical debridement. While appropriate antibiotic therapy is important in the management of this disease, medical therapy should be considered an adjunct to, not a substitute for, early aggressive surgical management.

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## Postoperative Dehiscence Following Gastric Banding Surgery

**Chapter:** Postoperative Dehiscence Following Gastric Banding Surgery
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 55-year-old woman with no significant past medical history underwent gastric banding surgery for weight loss. Three years later, she had erosion of the lap band into the gastric wall, and the lap band was surgically removed. Postoperatively, she underwent bedside debridement and over the next several months developed dehiscence of the wound, with formation of sinus tracts and abscesses with significant drainage. One year later, she required further debridement, and infectious disease consultation was prompted by the results of operative cultures.

She reported generalized malaise, fatigue, and a 10-pound weight loss over a period of one year, but denied fevers and chills. On physical examination, she had impending dehiscence of the wound with mild tenderness around the surgical site (Figure **11c.1**). Cultures of purulent material sent from the operating room grew Gram-positive, beaded bacilli after 7 days of incubation (Figure **11c.2**), and blood cultures also grew the same organism (Figure **11c.3**).





Figure 11c.1
Impending dehiscence of the midline abdominal wound.

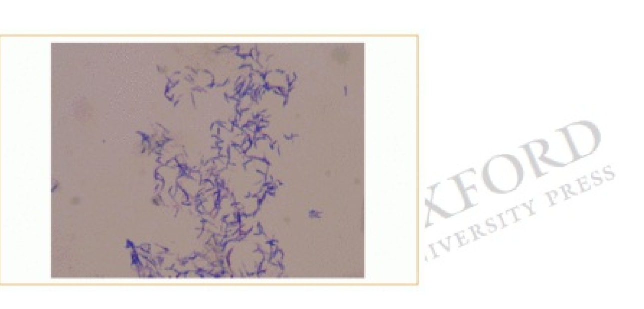




Figure 11c.2
Wound culture Gram stain showing Gram-positive, beaded bacilli.

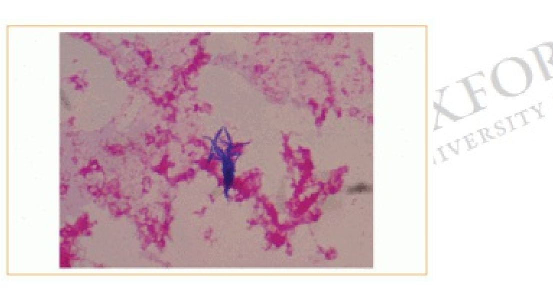




Figure 11c.3
Blood culture Gram stain showing Gram positive bacilli that were clumping in culture.

Both wound and blood cultures were later identified as the rapid-growing mycobacterium *Mycobacterium fortuitum* (Figures **11c.4** to **11c.6**). The patient was treated initially with intravenous clarithromycin, imipenem, and amikacin until the

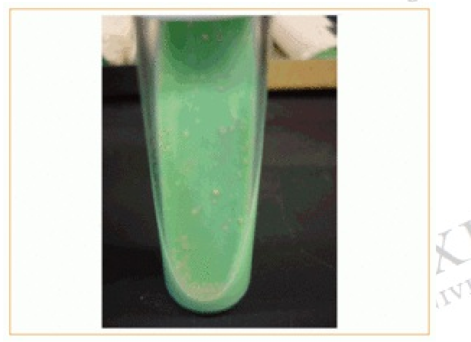




Figure 11c.5
Lowenstein-Jensen media with dry colonies of *Mycobacterium fortuitum*.

isolate was confirmed to be susceptible to amoxicillin/clavulanate and clarithromcyin. She required several procedures for surgical debridement, and was treated with oral antibiotics for 9 months, but eventually had satisfactory wound closure.







Figure 11c.4
Sheep's blood agar with dry colonies of *Mycobacterium fortuitum*.

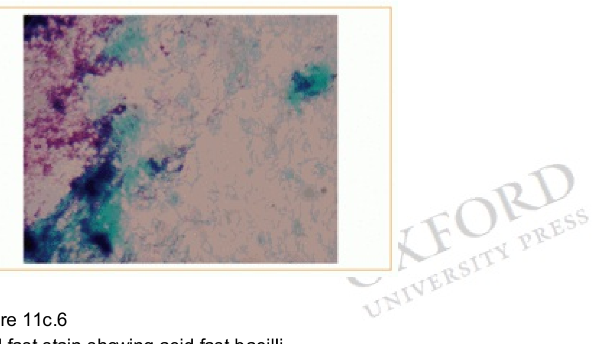




Figure 11c.6
Acid-fast stain showing acid-fast bacilli.

**Case 11c Discussion: *Mycobacterium fortuitum***

Nontuberculous mycobacteria (NTM) are composed of mycobacteria other than the species of *Mycobacterium tuberculosis* complex (*M. tuberculosis, Mycobacterium africanum, Mycobacterium bovis,* and *Mycobacterium leprae).* Originally known as atypical mycobacteria, they have become the focus of more interest over the past few decades due to their role in an increasing number of infections. NTM are found in the environment in soil, water, animal, and plant material, and will sometimes stain as Gram-positive, beaded bacilli. They are slender, nonmotile, acid-fast bacilli, and have traditionally been classified by the Runyon system of classification. This categorizes NTM into different groups based on growth rate, colony morphology, and pigmentation. Rapidly growing mycobacteria (RGM) describe nontuberculous mycobacteria that produce growth

on media plates in 7 days. The nonpigmented RGM include *M. fortuitum, M. chelonae/abscessus group, M. mucogenicum group,* and *M. smegmatis* group. The fifth group are pigmenting RGM that can be difficult to identify, and include several lesser-known species. Slowly growing mycobacteria take more than 7 days to grow, and the major species in this group include members of the *M. avium* complex, *M. kansaii, M. xenopi,* and other lesser-known species. *M. ulcerans* is also a member of this group, and is a major cause of cutaneous infection in Africa and Asia. *M. marinum* and *M. gordonae* are pigmented and are considered intermediately growing mycobacteria because they require 7–10 days to mature.[1]

Six different clinical syndromes caused by NTM have been described, including pulmonary infection, lymphadenitis, skin and soft tissue infections, disseminated disease, catheter-related infection, and infection of the tendon sheaths, bones, bursae and joints.[1] This review will focus mostly on skin and soft tissue infections caused by the nontuberculous mycobacteria.

Many of the NTM species have been implicated in causing cutaneous disease. The most common species to cause skin and soft tissue infections in the United States and Europe is *M. marinum. M. marinum* traditionally causes infection known as “swimming pool” or “fish tank” granuloma. It is associated with skin lesions that develop at the site of trauma after cleaning a fish tank or aquarium. Lesions usually involve the extremities— the finger is the most common site—and can spread up proximally in a sporotrichoid pattern. The lesions can be superficial nodules or ulcers, but may progress to disseminated or deep infections involving tendons, bones, joints, and bursae. No specific treatment guidelines exist for *M. marinum* infections, but treatment regimens usually involve single or dual therapy with clarithromycin, rifampin, ethambutol, doxycycline, or trimethoprim-sulfamethoxazole. Antimicrobials are continued for several months, with at least 4 to 8 weeks after resolution of lesions.[1] *M. ulcerans* is a slow-growing, nonpigmented, nontuberculous mycobacteria that causes African Buruli ulcer and Bairnsdale ulcer; it is a common cause of cutaneous disease worldwide. It is not found in the United States, but is found in warmer climates in Australia, Africa, Mexico, and Indonesia. It enters the skin at sites of trauma, and lesions ulcerate with extensive undermining of the ulcer. Buruli ulcer is principally treated with surgical excision, but adjunctive antimicrobials, including rifampin, amikacin, or streptomycin, are also used.[2]

The rapidly growing mycobacteria, specifically *M. abscessus, M. chelonae* and *M. fortuitum,* are among the most common NTM involved in cases of skin and soft tissue infections in the United States. Localized infections with *M. chelonae* and *M. abscessus* tend to cause disease in immunosuppressed hosts, whereas *M. fortuitum* usually causes infection in previously healthy individuals. In a retrospective medical review conducted at the Mayo Clinic, 63 patients with *M. chelonae, M. abscessus,* or *M. fortuitum* skin or soft tissue infection were compared. Patients with *M. chelonae* or *M. abscessus* were significantly more likely to be older or taking immunosuppressive medications, as compared to patients with *M. fortuitum* infection. More patients with *M. fortuitum* infection were likely to have had prior invasive surgical procedures.[3]

Many case studies of healthcare-associated infection with *M. chelonae, M. abscessus,* and *M. fortuitum* after surgical procedures have been described. These include outbreaks associated with hemodialysis, peritoneal dialysis, central venous catheters, acupuncture, liposuction, silicone injection, augmentation mammoplasty, cardiac bypass surgery, and dermatologic surgery.[3] Typically, the surgical devices or equipment used are contaminated from tap water or ice water.

While traditionally, skin and soft tissue infection with rapidly growing mycobacteria are hospital acquired, community-associated infections have been on the rise. Recently, Winthrop et al. described a large outbreak of *M. fortuitum* infections among clients receiving footbaths and pedicures at a nail salon in California.[4] They identified 100 customers of the nail salon who developed furunculosis, and cultures from 34 patients were positive for rapidly growing mycobacteria. In this outbreak, cultures from all the footbaths at the salon yielded *M. fortuitum,* and isolates from 3 of the footbaths and 14 patients were identical by pulsed-field gel electrophoresis.

Cutaneous infections secondary to rapidly growing mycobacteria were recently described as a complication of mesotherapy, a cosmetic dermatological procedure. Sixteen patients were infected after mesotherapy injections from the same physician; *M. chelonae* was identified in 11 patients and *M. frederiksbergense* was identified in 2 patients. Patients presented with painful nodules that progressed to fistulizing skin lesions with purulent drainage, about 9.5 weeks after the first mesotherapy procedure. All patients underwent surgical procedures to drain existing abscess and resect nodules; the majority received dual or triple antibiotic therapy for a mean duration of 14 weeks.[5]

Treatment can be challenging in patients with cutaneous infections secondary to rapidly growing mycobacterial infections, and usually involves multiple antimicrobials in order to minimize the risk of development of resistance. No controlled clinical trials of treatment have been conducted, and most recommendations are based on case studies and clinical experience along with in vitro susceptibility data. The majority of patients require a combination of prolonged duration of antimicrobial therapy for several months, and surgical excision or drainage and removal of any foreign devices that become infected, (e.g., implants or catheters).

In susceptibility testing done by Uslan et al., of 14 isolates of *M. fortuitum* and 47 isolates of *M. chelonae* or *M. abscessus,* 100% of isolates of *M. fortuitum* were susceptible to amikacin, as opposed to only 64% of *M. chelonae/M. abscessus* isolates. Susceptibility testing of *M. fortuitum* isolates found that the majority of isolates were also sensitive to imipenem and ciprofloxacin (70% and 86% respectively). For the *M. chelonae/M. abscessus* isolates, 100% were sensitive to clarithromycin and 80% were susceptible to tobramycin. This data therefore supports the use of amikacin as first-line therapy for *M. fortuitum* infection, and clarithromycin for *M. chelonae* or *M. abscessus* infection.[3]

According to most guidelines,[1, 6] *M. fortuitum* infections are usually susceptible to amikacin, imipenem, cefoxitin, ciprofloxacin, oxazolidinones, sulfonamides, and doxycycline. For *M. chelonae* infections, various combinations of amikacin, imipenem, tobramycin, and clarithromycin are usually recommended, and for *M. abscessus* infections, amikacin, cefoxitin, imipenem, and clarithromycin usually have activity. While macrolide treatment is recommended for *M. chelonae* or *M. abscessus* infection, and sometimes is used as monotherapy in mild infections, inducible resistance has been demonstrated; therefore, monotherapy should be undertaken with caution. Given the variability among clinical isolates, susceptibility testing should be used to guide treatment in individual cases.

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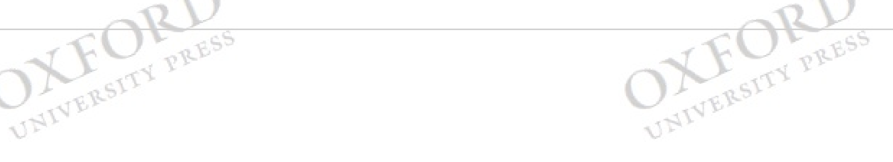
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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 61-Year-Old Woman from Mexico with Cutaneous Ulcers

**Chapter:** A 61-Year-Old Woman from Mexico with Cutaneous Ulcers
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 61-year-old female from Mexico presented with ulcerative skin lesions that were not improving despite empiric antibiotics. She had been treated with trimethoprim-sulfamethoxazole for presumed MRSA infection with no improvement. Initially she had two or three lesions on her thighs and arms that began as a pimple, and later ulcerated. She had been in the United States for two months, but had previously been working for a mulch company in Mexico.

On physical examination, she had multiple 2cm ulcerated erythematous lesions on her upper and lower extremities (Figure **11d.1**). The remainder of the physical examination was unremarkable, and laboratory values were notable for mildly elevated liver enzymes and positive hepatitis C serology. She reported having had similar lesions in Mexico. She had seen a physician and was told that she had a fungal infection, but she could not afford the therapy.



Figure 11d.1
Multiple 2cm ulcerated erythematous lesions on the upper and lower extremities.

Skin biopsy cultures results subsequently grew *Sporothrix schenckii,* and further evaluation revealed no evidence of disseminated disease. She was treated with itraconazole, with instruction to monitor liver function tests weekly.

**Case 11d Discussion: *Sporothrix schenckii***

#### Clinical Manifestations

Sporotrichosis is caused by the temperature-dependent dimorphic fungus, *Sporothrix schenckii*, and was first described in 1898 by Benjamin Schenck when he was a medical student at Johns Hopkins University.[1] The fungus is found worldwide in soil, plant, or plant products. Most cases are reported from the tropical and subtropical regions of the Americas. The infection generally is introduced into the dermal layer of the skin through a minor penetrating injury (e.g., by a thorn prick). An abscess and subsequent lymphangitic spread may ensue. The fungus may also disseminate hematogenously and cause extracutaneous lesions of the bones, joints, CNS, or eyes, in immunocompetent hosts, or multifocal disease in immunocompromised patients. Pulmonary infection in some patients may also be acquired via inhalation. Sporotrichosis usually affects healthy individuals engaged in outdoor activities, such as florists, rose gardeners, and horticulturists. Cases of animal-to-human transmission have been reported.[2]

Lymphocutaneus sporotrichosis is the most common form of sporotrichosis. A painless, papulonodular, erythematous lesion develops at the site of the infection days to weeks after inoculation of the fungus. The lesion may be smooth or verrucous, but usually ulcerates with a raised border. If there is drainage from the lesion, it is usually not purulent, and systemic symptoms are generally absent. Secondary lesions may develop proximally along lymphatic channels without contiguous spread or lymph node involvement. The lesions are usually indolent, waxing and waning over months to years if not adequately treated. Other organisms, including *Leishmania*, *Nocardia*, and nontuberculous *Mycobacteria* (particularly *M. marinum*) can present with “sporotrichoid” lymphangitic spread. Fixed sporotrichosis with indurated hyperkaratotic plaques has clinical overlap with other fungal infections, such as blastomycosis and paracoccidioidomycosis, as well as noninfectious causes such as malignancies, psoriasis and pyoderma gangrenosum.[1]

## Diagnosis

Culture of aspirated material from a lesion or a tissue biopsy is the gold standard of establishing the diagnosis. The usual histopathologic picture is that of a mixed granulomatous and pyogenic process. *Sporothrix* may be difficult to detect in histopathology, but PAS and GMS stains may improve visualization of the characteristic 1- to 3-μm × 3- to 10-μm cigar-shaped yeast forms organism. In some cases a central rounded yeast structure with radiating eosinophilic substance in tissue (asteroid bodies) can be seen on histopathology. Blood cultures are rarely positive except in the disseminated form of sporotrichosis seen in immunocompromised hosts.

## Treatment

For lymphocutaneous and cutaneous sporotrichosis, itraconazole 200mg daily is continued for 2 to 4 weeks after all lesions have resolved, usually for a total of 3 to 6 months. Alternative treatments in case of relapse include itraconazole at a higher dose of 200mg twice daily, or terbinafine 500mg twice daily, or saturated solution of potassium iodide (SSKI). Potassium iodide solution therapy begins with 5 to 10 drops taken orally three times daily. The dose is gradually advanced to 25–40 drops three times daily for children, or 40–50 drops three times daily for adults.

Fluconazole has only modest clinical activity, and should only be used if other therapies are not tolerated. Newer triazole antifungals have some in vitro activity, but little clinical data with these agents is currently available. Heat has been used as adjunct therapy and, on occasion, has been curative. It may be considered in pregnancy, since itraconazole and iodides are both potentially teratogenic. Monitoring of itraconazole blood levels is usually recommended only for systemic disease, or in HIV patients.[3]

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## Enlarging Skin Lesions in a Kidney–Pancreas Transplant Recipient

**Chapter:** Enlarging Skin Lesions in a Kidney–Pancreas Transplant Recipient
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 53-year-old man with a history of a diabetes mellitus presented with a 5-month history of painless, progressively enlarging left knee and calf skin lesions. He had undergone a combined pancreas and kidney transplant 18 months prior to presentation, but his post-transplant course had been complicated by several bouts of acute rejection. The most recent episode occurred one month prior to the onset of his skin lesions, and was managed with high-dose intravenous corticosteroids, thymoglobulin, and intravenous immunoglobulin in addition to his maintenance immunosuppressive regimen of mycophenolic acid 900mg twice daily, tacrolimus 2 mg twice daily, and prednisone 50 mg daily.

His physical examination was notable for a 3x3 cm erythematous, scaly lesion on his left knee, and a smaller hyperpigmented subcutaneous and cutaneous lesion on the left calf (Figure **11e.1**). Neither lesion was tender to palpation. Prior to his arrival at the infectious diseases clinic, the patient had undergone two biopsies of his knee lesion. Pathology from the first biopsy showed a moderately differentiated squamous cell carcinoma, but because of continued enlargement of the lesion, a second biopsy was performed. Histopathology of the second specimen revealed cutaneous fungal infection with pseudoepitheliomatous hyperplasia (Figures **11e.2**), and fungal culture from the biopsy grew *Alternaria sp.* He was treated with voriconazole, his immunosuppressive regimen was decreased, and he eventually underwent excision of the entire lesion with placement of an overlying skin graft.






Figure 11e.1
3x3 cm erythematous, scaly lesion on the left knee.

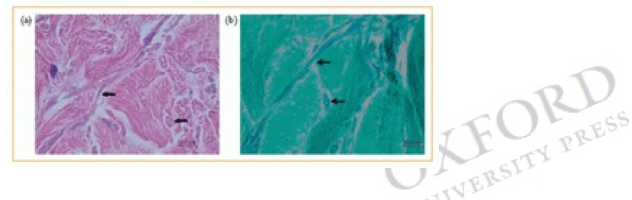



Figure 11e.2
Knee biopsy of tissue-invasive cutaneous *Alternaria sp.* infection with hyphal elements seen on both H&E (a) and GMS staining (b).

### Case 11e Discussion: *Alternaria*

*Alternaria* is a dematiaceous (melanized) mold that is one of the agents of phaeohyphomycosis. Infections with this heterogeneous group of fungi are increasing in frequency as

more patients are treated with immunosuppressive medications, such as those used in organ transplantation. The *Alternaria* genus encompasses hundreds of species with a worldwide distribution. *Alternaria* species are ubiquitous in nature, and are found in the soil, air, in plant decay, as a plant pathogen, and as normal flora on the skin of humans and animals.

A major portion of the *Alternaria* literature focuses on its association with hypersensitivity pneumonitis, bronchial asthma, and allergic sinusitis and rhinitis. In the immunocompromised host, however, cutaneous, subcutaneous, paranasal sinusitis, soft palate, disseminated disease and, very rarely, granulomatous pulmonary manifestations are encountered. Biopsy and culture are needed for diagnosis in these settings. It is a frequent agent of onychomycosis (owing to its ubiquitous presence in soil), and a cause of ocular infections after penetrating trauma or in contact lens wearers.

## Clinical Manifestations

### *Oculomycosis*

The incidence of this clinical manifestation of *Alternaria* infection varies across geographic regions, but its highest incidence is in India. Those with the greatest risk of ocular trauma due to organic matter have the highest incidence of disease.[1] Case reports and series document infections from traumatic injury from wheat or rice stalks, and even some from cow tails. Ocular infection most often leads to keratitis or endophthalmitis.[1] Studies have shown that *Alternaria* can remain dormant in the superficial layer of the cornea for long periods of time after trauma, and progress when the temperature allows for growth. This may account for several reports of keratitis several years after trauma.

### *Rhinosinusitis*

Symptoms of rhinosinusitis are generally minimal and are often found upon evaluation of unexplained fever. Seventeen case reports/series of invasive and noninvasive sinusitis caused by *Alternaria* spp. have been reported since 1977, though this likely greatly underestimates the true number of cases.[1] The majority of these cases have been reported in the United States in patients suffering from hematologic malignancies. In the majority of the cases, the organism was not identified to the species level.

### *Cutaneous and Subcutaneous Infections*

Cutaneous infections are the most common manifestations of *Alternaria*, significantly more frequent in occurrence than subcutaneous infections (88.4% vs. 5.8%).[1] Concomitant cutaneous and subcutaneous infections are rarely reported. Lesions can appear as shallow-based, nonhealing ulcers that evolve from nodules, subcutaneous noninflammatory cysts, verrucous-like lesions, or erythematous, confluent, scaly patches. Disseminated alternariosis can present with papulonodular lesions or cutaneous nodules.

The majority of patients manifesting this disease are immunosuppressed (84%), with the greatest number of cases seen in the solid organ transplant population (kidney)liver).[1, 2] The major risk factor in this group, as well as other immunosuppressed individuals, is systemic steroid use, possibly due to a combination of its immunosuppressive properties and through skin breakdown.[2] Along with the risk factor of an immunosuppressed state (solid organ or bone marrow transplant, immunosuppressive therapy, especially steroid use, Cushing's disease), many infected patients are able to identify a traumatic event leading to the infection.[1] Rarely, patients develop coinfection with other fungi; there are case reports of coinfection with *Phaeosclera* and *Scopulariopsis*.[3] Infection does occur in patients without known immunosuppression other than diabetes as a risk factor. Recurrence of nodules/infection after appropriate treatment, and after apparent clearing of the infection, has been described, including one case report of a patient with multiple recurrences spanning from 1942–1996.[4]

## Treatment

There is no standardization in the treatment of cutaneous alternariosis. In vitro studies indicate that itraconazole, and newer triazole antifungal show good activity.[5] Amphotericin B and ketoconazole have variable activity, while flucytosine and fluconazole have no activity.[5] In the clinical literature, the vast majority of cases have been treated with itraconazole with overall success, though treatment failures are also reported. More recent clinical reports indicate that newer triazole antifungal agents are a viable option for ocular, cutaneous, and disseminated disease. For successful cure in the immunocompromised patient with a large fungal load, whether cutaneous or sinonasal, surgical debridement is often needed in combination with prolonged antifungal therapy (6–12 months).[1] A concomitant dose reduction in the immunosuppressive regimen is suggested as well.

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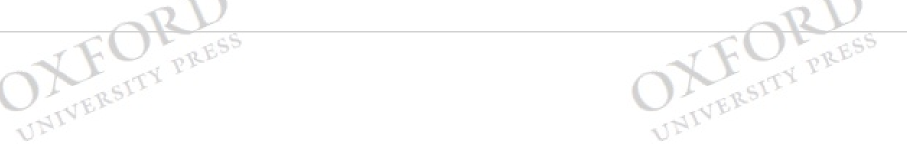







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## Orbital, Ear, and Skin Lesions in a Healthy Laboratory Research Assistant

**Chapter:** Orbital, Ear, and Skin Lesions in a Healthy Laboratory Research Assistant
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Presentation

A 24-year-old male presented in July with swelling and pain of his right ear and left eye. Six days prior to admission, the patient was stung by a bee on the left hand while vacationing in North Carolina. He subsequently developed swelling and pain of his right ear lobe, followed the next day by swelling around his left eye. The swelling at both sites worsened over several days, and small white dots formed on the right ear lobe. He had trouble seeing that he attributed to the swelling of his eyelids, which was accompanied by an opaque, yellow discharge. He described malaise and subjective fevers, and his symptoms did not respond to cephalexin and prednisone. He presented to the emergency department where he was noted to have some pain with eye movement, and he was admitted with a presumed diagnosis of orbital cellulitis. The patient denied any past medical problems, and had tested negative for HIV a few months prior to admission. He worked as a cancer and immunology research assistant at a hospital-affiliated research laboratory.

On physical examination, the patient was afebrile but in obvious discomfort due to right ear and eye pain. The lobe of his right ear was coated in crusted, purulent material, with a crop of vesicles inferior to his ear (Figure **11f.1a**). The vesicles were all at the same stage of development. His left periorbital soft tissue was edematous and erythematous (Figure **11f.1b**). A thick purulent discharge covered his sclera and cornea. There was no scleral injection. Pupils were equal, round, and reactive to light when the left palpebrae were parted. There was some pain with extraocular movement but no proptosis. Other cranial nerve functions were intact. His left hand (the reported site of the bee sting) had no lesions, but there were two small vesicular lesions on his chest and one on his flank. There was erythema of the skin surrounding each vesicle, but the remainder of his physical examination and laboratory studies was normal.

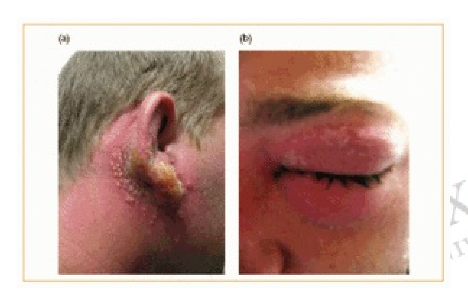





Figure 11f.1
(a) Lobe of his right ear showing crusted, purulent material with a crop of vesicles inferior to the ear; and (b) The left periorbital soft tissue was edematous and erythematous.

CT scan of the left orbit showed severe inflammation restricted to the preseptal tissues. The consulting ophthalmologist described conjunctivitis and blepharitis, with possible mild keratitis. Cellular culture of a swab taken from the purulent exudate from his eye showed a cytopathic effect (Figure **11f.2**). Polymerase chain reaction for vaccinia virus was performed on the cultured material and was positive. When the diagnosis was suspected, the patient's lesions had already begun to improve and, thus, systemic therapy was not required. The patient recovered with some madarosis but without visual sequelae.





Figure 11f.2
Cellular culture of a swab taken from the purulent exudate from the eye showed a cytopathic effect.

**Case 11f Discussion: Vaccinia Virus Infection**

## Clinical Features

Live vaccinia virus, an orthopoxvirus, is the immunogenic component of the smallpox vaccine, which is used to induce immunity to variola, the causative agent of smallpox. Since routine civilian vaccination was stopped in 1972, vaccination has been limited to those with a risk of exposure to orthopoxviruses through laboratory work or first response to a bioterrorist attack.[1] Intentional inoculation with vaccinia, for the purpose of vaccination, results in an inflammatory lesion that crusts and separates within approximately 14 days.[2] Live vaccinia is shed from the inoculation site for approximately 21 days. During this period, the virus may be transmitted to other susceptible individuals (accidental inoculation) or to other parts of the body of the vaccinated individual (autoinoculation). Covering the wound with a semipermeable dressing and adherence to hand-washing practices reduces the risk of transmission. In the described case, accidental acquisition from a laboratory animal had occurred, and subsequently spread to multiple sites, likely by autoinoculation.

Multiple complications of vaccination with vaccinia have been reported. Progressive vaccinia, or vaccinia gangrenosum, is fatal without treatment and occurs in infants and in immunocompromised hosts, usually with deficient cellular immune response. This severe disease is characterized by expansion of vaccinia lesions from the site of vaccination, or spread of lesions to distant sites.[3] There is a lack of inflammation, pain, or evidence of healing after 14 days. Lesions progress and develop into deep, necrotic ulcerations. Amputation of affected limbs is often required, and superinfection may occur. Eczema vaccinatum, a complication that occurred in 14–44 cases per million vaccinees prior to 1968, can occur in patients with atopic dermatitis even in the absence of active lesions or prior diagnosis of atopy. This complication may be acquired through vaccination or contact with a recently vaccinated individual, and manifests as either a localized or widespread, potentially fatal, cutaneous disease.[4]

In contrast to progressive vaccinia and eczema vaccinatum, generalized vaccinia occurs in immunocompetent individuals, and is a self-limited illness characterized by systemic symptoms and scattered vesicular lesions with surrounding erythema indicative of a proper inflammatory response. Postvaccination encephalomyelitis carries a high rate of death (up to 30%) and permanent neurologic sequelae (up to 20%). Myopericarditis may complicate vaccination, and was reported more frequently during military and civilian vaccination programs in 2003, instituted in response to the threat of bioterrorism. During this period, attention was also drawn to a risk of postvaccination cardiac ischemic events in patients with preexisting cardiac risk factors.

As in the case above, ocular manifestations occur as a result of accidental inoculation or autoinoculation. Blepharitis and conjunctivitis do not frequently result in serious long-term sequelae. While long-term sequelae are more likely to occur after keratitis (18%), the largest prospective study of vaccinia keratitis found minimal residual corneal defects 5 years after infection in the 7 patients that were available for evaluation.[5]

## Diagnosis and Treatment

Polymerase chain reaction of infected exudate is used for definitive, molecular diagnosis. Electron microscopy can be used to identify intracellular viral particles after growth of the virus in cell culture. The typical cytopathic effect of vaccinia consists of rounding, granularity without vacuolation, and expanding cytolysis with fibrinous material at the site of dead cells.

Vaccinia immune globulin (VIG) has decreased mortality from severe complications, with the exception of vaccinia-induced encephalitis. VIG is contraindicated in cases of isolated vaccinia keratitis, because it may increase the likelihood of corneal scarring, although the data are mixed. Cidofovir, and the experimental antiviral, ST-246, have in vitro activity against vaccinia and have been used in combination.[6] Topical trifluorothymidine and vidarabine are active against vaccinia in vitro, and are used to treat keratitis. Progressive vaccinia requires combined therapy with VIG, antiviral medications, and aggressive debridement.

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## A 46-Year-Old Man with Fevers, Rash, and Malaise

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### Case Presentation

A 46-year-old man presented to the emergency department with sore throat, abdominal pain, fever, and a diffuse erythematous rash that began 5 days prior to presentation. He also noted headaches, diffuse myalgias, joint pains, nausea, and diarrhea that began the previous day. On physical examination he was febrile (38.8°C), generally ill-appearing, and had enlarged erythematous adenoids, and cervical lymphadenopathy. The blanching, erythematous maculopapular rash was not pruritic, and involved his trunk, back, face, and extremities, including his palms (Figures **11g.1 and 11g.2**).





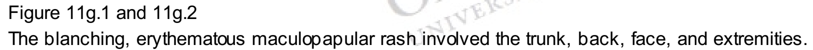


Figure 11g.1 and 11g.2
The blanching, erythematous maculopapular rash involved the trunk, back, face, and extremities.

The patient was originally from Beijing, China, and had arrived in New York 2 months prior to presentation. He had no sick contacts at the time of presentation, and he reported his only sexual partner was his wife in China. His laboratory values were notable for thrombocytopenia (99,000 cells/μl) and slightly elevated liver enzymes (AST 51 units/liter, ALT 42 units/liter). The rapid plasma regain was nonreactive, and the HIV ELISA test was negative. The HIV viral load, however, was positive at 8,997,771 copies/ml. The patient later admitted to having recently tried intravenous heroin using a shared needle. He was referred to a center conducting a clinical trial on acute retroviral syndrome.

#### Case 11g Discussion: Acute Retroviral Syndrome

##### Clinical Presentation and Diagnosis

The signs and symptoms associated with acute HIV infection may occur in 40%–90% of patients from 2 to 6 weeks after exposure.[1] Typically, patients present with an infectious mononucleosis-type illness, and symptoms include fever, pharyngitis, weight loss, myalgias, night sweats, headaches, nausea, and diarrhea.[1, 2] Patients may also present with a neurological picture consistent with aseptic meningitis. On physical exam, a morbilliform rash may be seen in 40%–80% of individuals.[2] In addition, generalized lymphadenopathy or mucosal ulcers may be present. Laboratory examination is notable in some cases for leucopenia, thrombocytopenia, and elevated liver enzymes.

Because symptoms are nonspecific, the diagnosis of acute HIV infection can be challenging; however, making the diagnosis of acute infection provides a crucial opportunity

for counseling and prevention of further transmission. There are four generations of HIV screening antibody tests used. The first-generation IgG sensitive indirect enzyme immunoassay (EIA) detects antibodies to viral lysate, and the second generation detects antibodies to recombinant synthetic peptide antigen. The first-generation EIA is no longer available for use in the United States. The third-generation EIA uses an antigen-antibody sandwich format, and detects both IgM and IgG antibodies, and is therefore positive earlier than first- or second-generation tests. A fourth-generation EIA combines detection of IgG and IgM antibodies along with p24 antigen, and is positive even before the third-generation test. The fourth-generation EIA is not yet approved for use in the United States.[3] The western blot is done to confirm a positive antibody test, but can often be negative or indeterminate in acute HIV infection.

Because these traditional HIV tests detect antibodies, there is a “window period” in acute HIV infection where these tests will be negative. These “window periods” are shorter in the newer-generation EIAs. In patients in whom acute HIV is suspected, an HIV-1 plasma RNA or viral load should be sent, in addition to antibody testing. HIV-1 RNA levels will be positive after 9 to 11 days in acute infection, and viremia can reach extremely high levels, up to several million copies, as in the case above.[4] HIV-1 RNA tests are highly sensitive and can have false positive results in up to 1% of cases; however, the viral load is usually low in these cases and this should prompt retesting. In the past, p24 antigen has also been used for diagnosis. While it is highly specific, it is not as sensitive as viral load testing, and false negative results limit its usefulness.[1]

While individual viral load testing can be expensive, pooled nucleic acid amplification testing (NAAT), in which specimens are pooled and then tested, is a strategy that has been effectively used by blood banks for screening. NAAT testing is now being adopted widely by many STD and public health clinics for screening high-risk populations. For example, patients presenting to 110 clinics in North Carolina for publicly funded HIV testing were screened using NAAT. In 8505 consecutive individuals screened, 39 were positive by traditional antibody screening and an additional five were RNA positive by pooled NAAT testing (one/five was a false positive result).[5] This strategy increased the diagnostic yield in this population by 10% compared with traditional antibody testing. Therefore, pooled NAAT may be an effective way of screening larger populations, and provides a unique opportunity for prevention.

## Management

The treatment of acute HIV infection with highly active antiretroviral therapy (HAART) remains a controversial topic. Those who advocate for early treatment hypothesize that it may serve as a unique opportunity to modify the host’s immune response to HIV-1. By preserving the HIV-1 specific cellular immune response, and decreasing the viral load set point, early initiation of HAART may delay or prevent decreased immune function and opportunistic infections. In addition, early therapy may mitigate symptoms of acute retroviral syndrome, and help prevent transmission by decreasing viremia.[1, 6]

While these are potential advantages, others argue that toxicities of treatment, development of resistance, and cost, remain reasons not to use HAART in acute HIV infection. In addition, duration of treatment in primary infection also remains unclear. Lastly, the above potential benefits of early HAART remain unproven in large randomized, placebo-controlled trials.

One of the initial randomized trials done, was conducted at a time when monotherapy for HIV was the standard of care. A multicenter, double-blind, placebo-controlled trial in which 77 patients with primary HIV were randomly assigned to receive either zidovudine or placebo for 6 months showed significant decrease in the number of opportunistic infections and a significant increase in the CD4 count in the zidovudine group; however, viral loads were not significantly different.[7] In addition, long-term follow-up over a period of 2 years showed that the initial clinical and immunological benefits seen seemed to wane over time, with differences between the two groups no longer remaining significant.

Subsequent trials have been mainly observational cohorts without much evidence to support treatment.[7, 8] Clinical trials are ongoing to assess the question of whether HAART in primary HIV infection would be beneficial. Currently, there are three major published guidelines that address this question. The United States Department of Health and Human Services (DHHS) guidelines recommend that treatment for patients with acute HIV is optional, and that the healthcare provider and patient should be aware that the rationale for treatment in acute HIV remains theoretical. They also recommend enrollment in a clinical trial. The International AIDS Society USA (IAS-USA) guidelines suggest that no evidence exists to support the initiation of antiretroviral therapy in acute HIV infection. The British HIV Association (BHIVA) guidelines also agree that conflicting evidence exists, and treatment should only be considered in patients with CD4 less than 200 or with an AIDS-defining illness. Therefore, until a large, placebo-controlled, randomized trial is done, the question of HAART during acute HIV infection remains controversial. At this time, most guidelines suggest that treatment is optional in this patient population, and that patients should be enrolled in a clinical trial.

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## 51-Year-Old Woman with a Painless Foot Ulcer

**Chapter:** 51-Year-Old Woman with a Painless Foot Ulcer
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 51-year-old woman with insulin dependent diabetes and end-stage renal disease was admitted with pneumonia and was treated with ceftriaxone and azithromycin. She also had painless, nonhealing left third toe ulcer that had been present for more than a month. The ulcer had no drainage, and she had not received any treatment for it previously. She denied any other symptoms, other than her presenting complaints relating to her pneumonia.

On physical examination, the patient was afebrile, and she had scattered wheezes in bilateral lung fields. Her extremity exam revealed palpable dorsalis pedis and posterior tibial artery pulses bilaterally, decreased sensation to fine touch in both feet, and a nondraining, nonerythematous ulcer at the base of the left third toe (Figure **12a.1**).






Figure 12a.1
Ulcer at the base of the left third toe

Laboratory values were significant for leukocytosis (11 × $10^3$ WBC/μL) and slightly elevated C-reactive protein (6.25 mg/l, normal (5). A swab of the ulcer had been sent for culture, and grew methicillin resistant *Staphylococcus aureus*. Plain radiography of the patient's left foot revealed a focal lucency at the third toe, suggesting bone erosion (Figure **12a.2**).










Figure 12a.2
Plain radiograph, left foot showing a focal lucency at the third toe suggestive of osteomyelitis

**Case 12a Discussion: Diabetic Foot Infections**

## Clinical Features and Diagnosis

Diabetic foot ulcers are common, and have been observed in up to 5% per year of patients with diabetes.[1] The vascular impairment and peripheral neuropathy of chronic diabetes contribute to both the development and progression of these lesions. Impairment of neutrophil function by hyperglycemia is also a contributing factor. The role of infection in diabetic foot ulcers is multifactorial, and soft tissue infections both in and around the ulceration are often present. The determination of whether an ulcer is infected is made clinically, based on the presence of drainage and erythema, as well as systemic signs such as fever. Laboratory markers of inflammation, such as elevated C-reactive protein and erythrocyte sedimentation rate, are also supportive of the diagnosis of infection.[2]

Although a variety of organisms may be responsible for infection in diabetic foot ulcers, aerobic Gram-positive cocci, such as *Staphylococcus aureus* and *Streptococcus* species are the most common pathogens.[2] Assessing the ulcer for bone infection is also an important part of the clinical evaluation. The likelihood of bone infection is significantly increased when bone can be probed within the wound.[3] Other imaging studies, such as plain radiography, nuclear studies (indium-labeled leukocyte scan combined with bone marrow imaging using technetium-99m–labeled sulfur colloid), or MRI may help to assess for the integrity of underlying bone when there is a high clinical suspicion of osteomyelitis, or if wounds persist.

## Treatment

Diabetic foot ulcers should be approached in a multidisciplinary manner with local wound care, as well as frequent wound surveillance.[4] There is little evidence to support the use of antimicrobial agents in ulcers that do not appear infected clinically. If clinical signs suggest infection in the soft tissue of the ulcer or surrounding tissues, then an antimicrobial course should be administered, with a duration based on perceived severity of infection. Broad-spectrum antibiotics are usually not necessary unless the infection is severe, although the presence of methicillin-resistant *Staphylococcus aureus* should be considered.[2] If underlying osteomyelitis is demonstrated or suggested, the wound should be surgically evaluated, with consideration for deep debridement in concert with extended antimicrobial courses.[5]

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## Non-Healing Skin Ulceration with an Associated Fistulous Tract

**Chapter:** Non-Healing Skin Ulceration with an Associated Fistulous Tract
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 54-year-old woman from Pakistan presented with a 16-month history of a non-healing ulcerative lesion at the base of her thumb, and a 2-month history of a draining tract at the thenar eminence. The patient recalled that the lesions began soon after a book fell on the dorsum of her thumb. It became progressively painful, with associated swelling of the thenar eminence and drainage of fluid. She denied any history of fevers, night sweats, cough, or weight loss.

On physical examination, all her vital signs were normal and her lungs were clear to auscultation. On the dorsal aspect of the first metacarpal bone on her right hand, there was evidence of a non-tender ulcerative lesion without associated erythema. The thenar eminence was slightly tender to palpation, with evidence of a draining sinus (Figure **12b.1**). Radiography of the wrist showed bony erosion of the base of the first metacarpal, base of second metacarpal, and trapezium (Figure **12b.2**), and chest radiography revealed evidence of apical scarring.






Figure 12b.1
The thenar eminence was slightly tender to palpation with evidence of a draining sinus.



Figure 12b.2
Radiography of the wrist showed bony erosion of the base of the 1st metacarpal, base of 2nd metacarpal, and trapezium.

A biopsy and swab of the ulcerative lesion were negative for acid-fast bacilli, but culture of both grew *Mycobacteria tuberculosis*. The patient was treated with isoniazid, rifampin, pyrazinamide, ethambutol, and vitamin B6. A subsequent chest CT scan showed no evidence of active disease, and all sputum samples were negative. The isolate was pansusceptible after the initial 2-month phase, and she was continued on isoniazid and rifampin. Because of bony destruction, slow healing, and an unstable joint, the patient underwent debridement with placement of a spacer. After 12 months of treatment, her thumb lesion appeared well healed (Figure **12b.3**) and treatment was

discontinued.









Figure 12b.3
Thumb lesion after 12 months of treatment.

**Case 12b Discussion: Tuberculous Osteomyelitis**

Worldwide, extrapulmonary *Mycobacterium tuberculosis* (MTB) represents 20% of all cases of TB, and infection of the musculoskeletal system represents 1%–5% of all tuberculosis cases.[1] It is thought to arise from a foci of bacilli lodged in bone during the original mycobacteremia of primary infection.[2] Any bone, joint, or bursa can be infected, but the spine, hip, and knee, in order of frequency, are the most common sites of infection. In addition to MTB infection, nontuberculous *Mycobacteria* (NTM) osteomyelitis, and osteoarticular infections occur, as well. NTM infections are more commonly seen in immunocompromised patients, or those that have experienced trauma or surgery; *M. marinum, M. bovis* after bCG vaccination*, M. avium-intracellulare, M. fortuitum, M. chelonae, M. ulcerans, M. kansasii, M. xenopi,* and *M. haemophilum* have all been documented as causes of musculoskeletal disease.[1,2]

## Clinical Presentation and Diagnosis

There has been an evolution in the presenting symptoms of osteoarticular TB within resource rich nations. Newer reports suggest that the majority of cases now affect an older population who present with more systemic symptoms, multiple joint involvement, and periarticular abscess formation, whereas previous literature suggested that it evolved as a chronic, slowly progressive monoarthritis, mostly affecting the hip or knee.[3] The most common sign is pain and local swelling at the involved joint, and fever and weight loss are present in only a minority of patients.[2] In chronic cases, cutaneous fistulae, abscesses, and obvious joint deformity may also be present.

Synovia and periarticular bone are usually involved at the time of diagnosis. Bony foci result in local demineralization and may destroy the epiphyseal plate, resulting in deformity to the affected limb.[4] Articular cartilage loss occurs as the infection spreads to subchondral bone and disrupts the nutritional supply of the cartilage.[4] Synovitis develops with resultant joint effusion, granulation tissue, and development of a pannus and erosions at the margins of the joint.[4] Necrotic cartilage and fibrinous material form the classic “rice bodies” found in synovial fluid.

The weight-bearing articular surfaces are often preserved early in disease, providing potential for functional recovery if treatment is initiated early.[4] Radiographic findings usually evolve weeks to months after symptoms, demonstrating osteopenia, periarticular bony destruction, periosteal thickening, and destruction of cartilage and bone. In chronic cases, cold abscesses and fistulous tracts form: 50% of vertebral osteomyelitis cases have paraspinal cold abscesses.[1]

Synovial leukocyte counts in tuberculous arthritis are typically lower than those found in bacterial septic arthritis, but biopsy and culture data are needed to confirm the diagnosis. In articular TB, the synovial fluid culture (sensitivity of 74%) is often nondiagnostic, whereas biopsy and culture of the synovium bone or deep tissue has a sensitivity approaching 95%.[2] Superficial cultures often demonstrate bacterial contamination and acid-fast smears are rarely positive. A finding of caseous granulomas on bone biopsy (found in 94% of cases) may be enough to begin empiric therapy in the right clinical setting.[2] The utility of molecular diagnostic tests in the assessment of smear-negative or culture-negative patients with suspected extrapulmonary tuberculosis remains unclear.[2] Tuberculin skin test results are variable, but chest radiography should be performed to evaluate for pulmonary involvement.

## Treatment

Medical therapy for bone and joint tuberculosis does not differ significantly from pulmonary disease (see Chapter 6). According to the CDC, initial four-drug combination therapy is recommended until susceptibilities are obtained, with increasing evidence that 6–9 month regimens that include INH and rifampin are effective.[5] Some experts recommend 12–18 months of therapy, particularly for poorly vascularized sites, such as bones and joints.[4,5] Prolonged therapy should be considered for patients slow to respond to otherwise adequate treatment. The treatment of drug-resistant disease follows the same principles for treatment of other sites. Surgical debridement is not needed for cure, but it may help decrease the load of bacilli. If a joint is unstable or significantly damaged, fusion or replacement may be necessary. In those cases, prolonged medical therapy should be used prior to and at times, after, replacement.[4]

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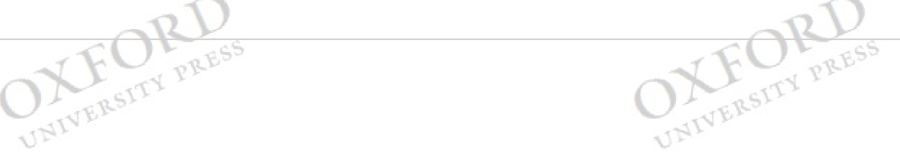



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## A Painful, Swollen Knee

**Chapter:** A Painful, Swollen Knee
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### Presentation and Case History

A 72-year-old woman with a history of hypertension and osteoarthritis underwent a total knee replacement of the right knee. Six months later she presented with severe pain, swelling, and warmth of the right knee for 2 days. She also had shaking chills, subjective fevers and progression of the pain to the point that it was limiting her ability to stand or ambulate. On physical examination, she was afebrile, but the right knee was very tender, swollen, and warm (Figure **12c.1**).





Figure 12c.1
Swollen right knee several months after knee replacement.

Her laboratory examinations were notable for elevated C-reactive protein (199mg/l, normal ⟨5) and erythrocyte sedimentation rate (78 mm/hour, normal ⟨20), but her peripheral white blood cell count was not elevated (8 × $10^3$ WBC/μl). Aspiration of the knee revealed cloudy pink fluid with 102,000 WBC/μl, 90% polymorphonuclear cells. No organisms were seen on Gram-stain, but the fluid culture was positive for *Streptococcus intermedius*.

During intubation for removal of the prosthesis, the patient was noted by the anesthesiologist to have gross periodontal disease with a crumbling right upper molar and a periapical abscess. The prosthetic knee was removed, the space debrided, and an antibiotic-coated spacer was placed. Cultures from the operating room also grew *Streptococcus intermedius*, and the patient revealed that several of her teeth had been loose, but that she was afraid of dentists. The remaining necrotic tooth was extracted and she was treated with intravenous ampicillin/sulbactam for 8 weeks. Upon removal of the antibiotic-coated spacer, excessive bleeding did not allow for a new prosthesis and a new spacer was placed instead. All cultures from the subsequent surgery were negative, and a new prosthesis was finally placed 3 months after the removal of the original prosthesis.

#### Case 12c Discussion: Prosthetic Joint Infections

Joint replacement surgery (arthroplasty) is a widely performed surgical procedure in the United States. In 2006, primary total hip and knee arthroplasties alone accounted for close to 800,000 of such cases. Besides infection, a number of other, noninfectious complications deserve mention; these are mainly mechanical in nature, and include aseptic loosening of the prosthesis, dislocation, and fracture of either prosthesis or adjacent bone. Even in the era of perioperative antibiotic prophylaxis, and optimized surgical environments using laminar airflow technique, prosthetic joint infections occur with infection rates ranging between 0.5% to 1.0% for hip replacements, 0.5% to 2% for knee replacements, and less than 1% for shoulder replacements. The frequency with which these procedures are performed produces significant case numbers, financial strain on the healthcare system (estimated cost of treating an infected arthroplasty is in excess of $50,000 per episode), and individual morbidity/disability.[1,3]

Risk factors for prosthetic joint infections include revision arthroplasty (either due to a mechanical complication/failure, or infection at the same site), rheumatoid arthritis, diabetes mellitus, poor nutritional status, obesity, smoking, concurrent immunosuppressive therapy (e.g., corticosteroids), concomitant malignancy, postoperative surgical site infection or wound healing complications (hematoma, dehiscence, wound necrosis, etc.), simultaneous bilateral arthroplasty, and prolonged operative time (⟩2.5 hours).[1,2]

Staphylococci (*S. aureus* and coagulase-negative *Staphylococcus* species) account for more than 50% of primary prosthetic hip and knee infections, but virtually every

microorganism can cause prosthetic joint infection. *S. aureus* is particularly common in patients with rheumatoid arthritis undergoing arthroplasty. *Propionibacterium acnes* is a rare cause of infection following hip and knee arthroplasty, but has been described in up to 16% of prosthetic joint infections following shoulder arthroplasty. Up to 20% of infections are polymicrobial, and up to 10% are culture-negative, commonly in the context of antimicrobial therapy prior to culture acquisition.[2,3]

The most common presenting symptom is pain. In acute infection, severe pain, swelling, erythema, and warmth at the site of the infected joint and fever are common. Chronic infection generally has a more subtle presentation, with pain alone, and is often accompanied by loosening of the prosthesis at the bone–cement interface, and sometimes by sinus tract formation with discharge. The pathogenesis of prosthetic joint infections is determined by a variety of factors, particularly the inoculum size and virulence of microorganism(s) involved, as well as host factors (integrity of immune function, impaired wound healing, etc.). Biofilm formation at the site of prosthetic surfaces is an important phenomenon in the establishment and persistence of microbial infection; it shields pathogens from the microbicidal effects of the host immune system, and provides relative resistance to antimicrobial therapy.[1]

Infections occurring early in the postoperative course (usually within 3 months of joint replacement) are typically acute in presentation and involve virulent organisms (e.g., *S. aureus* or Gram-negative bacilli) inoculated at the time of implantation. Patients who develop postoperative wound complications (e.g., dehiscence, necrosis, or hematoma) may also develop infection early on, by contiguous spread of organisms from the superficial wound to deeper soft tissue structures and prosthetic surfaces. In contrast, infection with less virulent organisms (e.g., coagulase-negative staphylococci and *P. acnes*) more commonly presents as chronic infection several months (or years) postoperatively. Acute hematogenous infection is characterized by the acute onset of symptoms of infection in a previously well-functioning joint. It can occur at any time following arthroplasty, even many years postoperatively. Transient staphylococcal bacteremia in one report led to secondary prosthetic joint infection in approximately one-third of cases. The primary focus of infection in such cases is unrelated to the prosthetic joint; the most common sites are skin and soft tissue, followed by dental (as is the case in the patient discussed above), and urinary tract. *S. aureus* and *S. epidermidis* are responsible for most infections, except for those originating in the urinary tract, where *E.coli* is the most common pathogen.[2,3]

Serologic inflammatory markers can aid in the diagnosis of prosthetic joint infection, while leukocytosis has a low sensitivity in detecting infection. In the absence of concomitant inflammatory conditions, C-reactive protein (CRP) measurement is a useful tool, with a sensitivity of 73% to 91% and a specificity of 81% to 86% for the diagnosis of prosthetic knee infection (using a cutoff of ≥13.5 mg/l). For the diagnosis of prosthetic hip infection, it has a sensitivity of 95% and a specificity of 62% (using a cutoff of )5 mg/l). While CRP level and erythrocyte sedimentation rate (ESR) are typically elevated following an uncomplicated arthroplasty, the CRP level usually returns to the preoperative level within 2 months; the ESR rate, however, may remain elevated for several months. CRP levels may be misleadingly normal in patients who have received antibiotics, or who have infection that is caused by low-virulence organisms (e.g. *P. acnes*).[1,3]

A synovial fluid leukocyte count of more than $1.7 \times 10^3$/μl, or a differential count with more than 65% neutrophils, is indicative of an infected knee arthroplasty. A synovial fluid leukocyte count of more than $4.2 \times 10^3$/μl or more than 80% neutrophils suggests an infected hip arthroplasty; these cutoffs are significantly lower than those used to diagnose native infectious arthritis. Synovial fluid cultures have a sensitivity of 56% to 75% and a specificity of 95% to 100% when directly inoculated into a blood-culture bottle.[2,3]

A variety of radiologic and nuclear medicine studies are available to assess the extent of osseous and soft tissue involvement, but in many cases do not reliably distinguish between infectious and noninfectious etiologies. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used imaging modalities. The nuclear medicine study considered to be the modality of choice with the highest specificity (98%) is labeled-leukocyte imaging (e.g., leukocytes labeled with indium-111) combined with bone marrow imaging (using technetium-99m–labeled sulfur colloid).[1]

Treatment of prosthetic joint infections is not standardized, because of the variable clinical presentations and the lack of data from randomized, controlled trials. Initial treatment success is often followed by relapse once antibiotics are discontinued—in part, due to biofilms sequestering the causative microorganism. Most patients with prosthetic joint infections ultimately require prosthesis removal for successful eradication of the infection. This can be accomplished in a one-stage procedure that involves removal of the infected prosthesis, debridement of the underlying bone, and placement of a new prosthesis during the same operation. Due to the risk of recurrent infection, such an approach may only be suitable in highly selected patients who have satisfactory soft tissue, no severe coexisting illnesses, and infection with organisms that are highly susceptible to antimicrobial medications.[2,3]

Two-stage arthroplasty appears to be the treatment modality with the highest success rate in patients who can tolerate prolonged periods of immobility. This procedure involves removal of the infected prosthesis, and debridement and culture of the underlying bone and periprosthetic tissues. A spacer impregnated with one or more antimicrobial agents may be used to maintain the leg at its correct length, and aid in controlling the infection. Intravenous antibiotics with activity against the infecting organisms are administered for at least 6 weeks. Reimplantation of a new prosthesis is usually undertaken following the 6-week course of antimicrobial therapy.[1]

The duration of antimicrobial therapy following implantation of a new prosthesis (either in the setting of a 1-staged or 2-staged approach) is not well defined, but a minimum of 4 to 6 weeks of antimicrobial therapy with proven efficacy against the isolated pathogen is considered to be the accepted standard of care. In patients undergoing debridement with retention of the prosthesis, 3-month courses of treatment for infection associated with hip prostheses, and 6-month courses for infection associated with knee prostheses, are often used. Oral therapy can be used if the agent has good oral bioavailability (e.g., quinolones, trimethoprim–sulfamethoxazole, and tetracyclines). Arthrodesis and amputation are measures of last resort, and long-term suppressive therapy alone is sometimes necessary in patients who are elderly, have contraindications to general anesthesia, or refuse to allow removal or debridement of an infected prosthesis.[2,3] IDSA guidelines addressing the issue of prosthetic joint infections are currently in progress, and expected to be published in the winter of 2011.

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## A 68-Year-Old Woman with Fever and Multiple Inflamed Joints

**Chapter:** A 68-Year-Old Woman with Fever and Multiple Inflamed Joints
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### Case Presentation

A 68-year-old woman from Puerto Rico presented with several days of shaking chills, weakness, watery diarrhea, arthralgias, and malaise. The pain had been in prominent in the joints of her fingers, and was accompanied by warmth, redness, and swelling on the day prior to admission. Her past medical history included insulin-requiring diabetes mellitus, hypertension, and hypercholesterolemia. The patient was a smoker, but denied any intravenous drug use, travel, recent antibiotic use, or sexual activity.

On physical examination, she was ill-appearing with a fever to 38.1° Celsius, hypotensive (blood pressure 98/50), and tachycardic (heart rate 114 beats per minute). Examination of her joints revealed erythema, warmth, edema, and tenderness over her left hand 2nd and 3rd metacarpophalangeal (MCP) joints and right hand 2nd MCP joints (Figure **12d.1**). Full flexion and extension were impaired in all MCP joints, and there was left wrist pain on active and passive movement. The remainder of her physical examination was unremarkable.



Figure 12d.1
Erythema, warmth, edema, and tenderness over the left hand 2nd and 3rd metacarpophalangeal (MCP) joints and right hand 2nd MCP joints.

Her laboratory analyses were notable for leukocytosis 24.5 × $10^3$ WBC/μl, thrombocytopenia (80 × $10^3$ platelets/μl), and elevated erythrocyte sedimentation rate (87mm/hour) and C-reactive protein (186 mg/l). Blood cultures were positive for *Neisseria meningitidis* (Figure **12d.2**), serogroup Y, and arthrocentesis of the MCP joints was attempted but unsuccessful. She was treated with 14 days of intravenous ceftriaxone followed by oral penicillin for 14 more days.

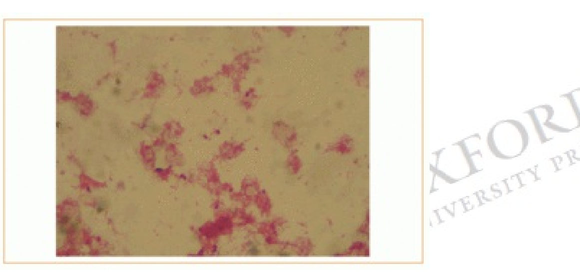


Figure 12d.2
Blood cultures Gram stain with Gram-negative diplococci later identified as *Neisseria meningitidis*.

**Case 12d Discussion: *Neisseria meningitidis***

*Neisseria meningitidis* is a Gram-negative aerobic diplococcus, first recovered in meningeal exudate 1887 by Anton Weichselbaum. The serogroups that cause the majority of disease are A B, C, Y, and W-135. These serogroups are based on antigenic variation of the polysaccharide capsule, and vary worldwide depending on geographic region. In North America, serogroups B, C, and Y are most common, whereas in Africa, particularly in the "meningitis belt," serogroups A, W-135, C, and X predominate.[1]

*Neisseria* grows best on chocolate agar, and exhibits a host of virulence factors, including its adherence to the microvillus surface of nonciliated columnar mucosal cells of the nasopharynx, its antiphagocytic polysaccharide capsule, and its endotoxin release. Major risk factors for infection include asplenia, deficiency of terminal complement components, household contacts, black race, low socioeconomic status, active or passive exposure to tobacco smoke, and crowded living situations. Several syndromes associated with meningococcal disease have been reported in the literature: meningitis, bacteremia, meningococcemia (fever, purpura fulminans, hypotension, Waterhouse-Friderichsen syndrome), pneumonia, epiglottitis, conjunctivitis, urethritis, septic arthritis, pericarditis, and chronic meningococcemia.[1]

The clinical syndrome in this particular patient was one of a native joint infection. In general, these infections are a result of occult bacteremia, but may also be caused by trauma. Gram-positive organisms are by far the most common cause, with *Staphylococcus aureus* being the pathogen in almost half of all native joint infections.[2] This is followed by *Streptococcus pyogenes* and *Streptococcus pneumoniae*. Gram-negative etiologies include *H. influenza, E. coli, Salmonella, N. gonorrhea* and *N. meningitidis*. In young adults, gonococcal arthritis is a leading cause of septic arthritis behind *S. aureus*.

Native joint infections commonly involve the knee joints. The classic clinical presentation of fever, leukocytosis, and joint pain may not always be present, particularly in immunocompromised patients. Diagnosis is often elusive, since Gram staining of synovial fluid is only positive in 71% of Gram-positive organisms[3] and 40% of Gram-negative organisms. Blood cultures may be helpful, as up to one-third of patients may have positive blood cultures. WBC counts in synovial fluid may be )50,000 cells/mm,[3] though counts as high as these may also be found in cases of gout and pseudogout. Many cases of septic arthritis have negative synovial fluid cultures, particularly in the case of gonococcal arthritis.

Our patient had a presumed case of meningococcal arthritis. Though rare, arthritis in meningococcal infection has been described as early as 1898 by Osler, when he reported it as "the arthritis of cerebrospinal fever" in a patient with arthritis and meningococcal meningitis. While our patient did not have meningococcal meningitis, she did present with arthritis in the setting of meningococcal bacteremia and disease. Typically, arthritis in meningococcal infection affects the knee joints more than the smaller hand and wrist joints. There is variation in the time of onset of arthritis from an acute presentation to up to one month after therapy.[4,5]

Three clinical types of arthritis have been described in meningococcal disease: arthritis as a complication of meningococcal disease, primary meningococcal arthritis, and arthritis as a complication of chronic meningococcemia. In the first syndrome, the knees and elbows are the most commonly affected, and synovial fluid is positive in only 15%–20% of patients. In contrast, primary meningococcal arthritis presents as an acute pyogenic arthritis with positive synovial fluid cultures and no signs of meningitis or meningococcemia. The peak incidence of this disease is in infancy, and there is a male predominance. Response to antibiotics alone is slow, and usually requires surgical drainage. The third syndrome, which is associated with chronic meningococcemia, presents more often as arthralgia than arthritis. There may be intermittent fevers for over a week, and a migratory rash without systemic toxicity. The pathogenesis is thought to be secondary to immune complex deposition.[5,6]

*Neisseria meningitidis* is exquisitely susceptible to beta-lactam antibiotics. Ceftriaxone 2g IV every 12 hours, or cefotaxime 2g IV every 4–6 hours, is the recommended first-line therapy for meningitis due to the organism. Alternative therapies include penicillin G, 4 million units IV every 4 hours.[6,7] Primary meningococcal arthritis should be treated with intravenous antibiotics, as well as surgical drainage; however, arthritis as a complication of meningococcal disease may not require surgical intervention in addition to antibiotic therapy. Because arthritis as a complication of chronic meningococcemia is thought to be due to an immune complex deposition, the role for long-term antibiotics remains unclear.[5]

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A Veterinarian with Multiple Skin Ulcers after Travel to Costa Rica

**Chapter:** A Veterinarian with Multiple Skin Ulcers after Travel to Costa Rica
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 32-year-old man returned from a 14-day vacation to Costa Rica with several ulcerative skin lesions on his left wrist, right and left flanks, and left leg. He also noted palpable nodules on his left arm proximal to the left wrist lesions. Besides the ulcers on his wrist (which began as papules), he also noted three ulcers on his flanks, as well as two on his lower legs. He did not recall any trauma to the areas, and initially thought the lesions were due to insect bites.

He had no prior medical history and had not traveled to destinations other than Costa Rica, and his work as a veterinarian mainly exposed him to dogs and cats. His itinerary included visits to the Arenal volcano region, as well as overnight stays in the Pacuare jungle lodges where he participated in outdoor activities including river rafting and ziplining. He had intermittently used insect repellant, and did not sleep under bed nets. He denied any systemic symptoms and was afebrile at the time of presentation to our travel medicine practice, 6 weeks after his initial skin lesions appeared. On physical examination, he had three coalesced ulcers on his wrist (Figure **13a.1**), two lesions on his left flank (Figure **13a.2**), one on the right flank, and two on the lower left leg. He also was noted to have a nodular subcutaneous lesion beneath the left bicep muscle, suggestive of lymphangitic spread from the wrist site.



Figure 13a.1
Cutaneous ulcers on the left wrist with raised erythematous borders. Proximal to the lesions, several subcutaneous lymph nodes were palpable.





Figure 13a.2
Cutaneous ulcer on the left flank.

Skin scrapings of the base of the lesion and biopsy revealed the presence of intracellular and extracellular *Leishmania* amastigotes with typical kinetoplast structures visible adjacent to the protozoan's nucleus (Figure **13a.3**). Cultures of the biopsy performed at the Centers for Disease Control subsequently were positive, and PCR testing confirmed that the species was *L. v. panamensis*. Prior to the confirmation of the culture results, the patient began therapy with oral miltefosine 50 mg orally, twice daily. The medication was obtained under a single-patient investigational new drug (IND) protocol under the supervision of the Food and Drug Administration, and imported from the manufacturer in Germany.

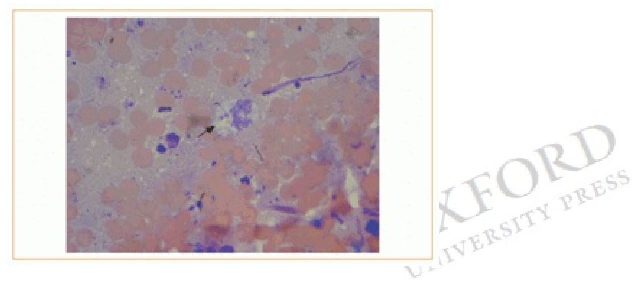


Figure 13a.3
Giemsa stained skin scrapings of the base of the lesion showing intracellular and extracellular *Leishmania* amastigotes with typical kinetoplast structures visible adjacent to the protozoan's nucleus.

During the treatment regimen, the patient experienced mild nausea on two occasions when he did not take the medication with food, but otherwise was able to complete the 28 days of therapy without adverse events. Several weeks later, the patient's lesions showed excellent healing and he experienced no further recurrences (Figures **13a.4** and **13a.5**).



Figure 13a.4
Wrist lesions several weeks after completion of treatment.





Figure 13a.5
Wrist lesions four years after treatment showing complete resolution.

**Case 13a Discussion: Leishmaniasis**

## Clinical Features and Diagnosis

Leishmaniasis is caused by the protozoan parasite *Leishmania,* and may present with a variety of clinical symptoms depending on the infecting species and the immune status of the host. The organism is transmitted to humans via the bite of a tiny insect vector known as the sandfly, and can cause disease in animal reservoirs such as dogs, foxes, and rodents in endemic areas. *Leishmania* is transmitted in a flagellated promastigote form, and is phagocytosed into tissue macrophages where it transforms into the amastigote form. The parasite is able to survive and replicate within immune cells, and lyses the cells as it multiplies. As the organism replicates in the tissue macrophages of the skin, the inflammatory response leads to a nodular lesion that erodes to become a painless ulcer. There is often a raised erythematous border surrounding the central ulceration, and proximal lymphadenopathy may be a sign of lymphangitic spread.[1] This presentation of the illness has clinical overlap with other infections, such as sporotrichosis and *Mycobacterium marinum* infections.

Certain species of the *Leishmania* genus cause cutaneous disease alone, and approximately one-third of patients with this form of the infection have ulcers that heal over time without treatment. In parts of Central and South America, other species can spread to the mucosal tissues of the oropharynx and nose, and lead to a highly disfiguring form of the disease called *mucocutaneous leishmaniasis*. Visceral leishmaniasis is caused by species found in South America, Africa, Southern Europe, and India. This potentially fatal form manifests with fevers, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia. Its tendency to cause a darkening of the skin led to the designation, Kala-Azar, a Hindi term meaning "black sickness."[1]

Leishmaniasis is widely distributed throughout the tropics, Middle East, South Asia, and Southern Europe. An estimated 12 million individuals suffer from the disease, and an estimated 2 million new cases of Leishmaniasis occur each year, with an annual estimated mortality of 70,000.[1] Leishmaniasis has principally been a disease of

impoverished nations in the tropics; however, reactivation illness in patients with AIDS has emerged as an important opportunistic infection in patients in southern Europe.[1]

The diagnosis of cutaneous leishmaniasis can be established by visualization of the intracellular or extracellular amastigotes on smears taken from superficial scrapings or punch biopsies of the ulcer. The kinetoplast is the intracytoplasmic body adjacent to the nucleus that distinguishes the amastigotes of *Leishmania* from the yeast cells of *Histoplasma capsulatum*. The organism can also be cultured from the scrapings or biopsied material when incubated on Novy-MacNeal-Nicolle (NNN) media. The use of polymerase chain reaction directly on tissue specimens has proven useful in many cases, and is performed in laboratories at the Centers for Disease Control and Prevention, and at the Walter Reed Army Institute of Research.[2] Serologic assays may have some clinical utility in travelers, but are often falsely negative, especially in cutaneous disease. Given the protean manifestations of the *Leishmania* genus, confirmation of the species can be especially important in decisions regarding treatment.

## Management

Standard systemic therapy for leishmaniasis in most parts of the world includes the intravenous infusion of the heavy metal, pentavalent antimony. The duration of treatment with this intravenous medication varies from 20–28 days, and the toxicities include muscle and joint aches, electrolyte abnormalities, and potential cardiotoxicity. In the United States, it is available only through the Centers for Disease Control and Prevention's antiparasitic medication branch. Amphotericin deoxycholate and lipid preparations of amphotericin have demonstrated efficacy in treating both mucocutaneous and visceral forms of leishmaniasis.[3] Single-dose liposomal amphotericin therapy has been effective in treating visceral leishmaniasis in the Bihar state of India, where resistance to antimonial medications remains an important problem.[4] The use of lipid preparations of amphotericin for cutaneous leishmaniasis have been extrapolated from studies in visceral leishmaniasis, and 5–6 doses of 5mg/kg of liposomal amphotericin B have yielded satisfactory results.[1]

New World cutaneous leishmaniasis has been an emerging infection among travelers, as travel to endemic regions has increased. Systemic treatment for cutaneous leishmaniasis is currently recommended for patients whose infections may be caused by species with the potential to cause mucocutaneous disease in the future. Because of the potential toxicities of the currently available parenteral therapies, oral agents such as miltefosine have generated increased interest. Miltefosine was originally developed as a chemotherapeutic agent, but it was discovered to have antiprotozoal activity by inhibiting phospholipid and sterol biosynthesis.[5] Its low toxicity profile and oral formulation make it an excellent agent to treat many forms of leishmaniasis. Studies of miltefosine for New World cutaneous leishmaniasis use indicate that it is more effective against the *L. v. panamensis* complex than against the *L. v. braziliensis* and *L. m. mexicana* subspecies.[5,6] Miltefosine is currently not routinely available in the United States except when imported via an investigational new drug protocol under the supervision of the Food and Drug Administration.

Prevention of leishmaniasis in travelers is mainly achieved through the use of insect precautions with N,N-Diethyl-meta-toluamide (DEET)-based skin repellents and premethrin-based clothing treatments. The usefulness of many bed nets is limited by the small size of the sandfly, although insecticide-treated nets can offer some protection against leishmaniasis in areas where the sandflies are predominantly nocturnal feeders. As leishmaniasis is also a zoonotic illness that can affect dogs and other small mammals, control of the disease in animal reservoirs is another potential intervention to reduce human disease. Dog collars treated with deltamethrin have been demonstrated to reduce the rate of canine disease, as well as human disease in children in areas in which the collars were used. Efforts to develop an effective vaccine against Leishmania have been hampered by the organism's species diversity, and mechanisms for intracellular survival and immune evasion.[1] Killed Leishmania vaccine combined with Bacillus Calmette-Guérin has had some limited efficacy in South American studies, but investigation is also ongoing in the development of live attenuated vaccines as well as novel antigenic targets.[1]

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## Fever in a Returned Traveler

**Chapter:** Fever in a Returned Traveler
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 30-year-old man from India presented to the emergency department with a 2-day history of fever, shaking chills, mid-epigastric discomfort, and diarrhea. The patient had lived between India and the United States over the past 2 years, and his last 6-month stay in India ended 6 weeks prior to admission. While in India, he presented to a local doctor due to fever and abdominal pain, and was treated empirically for both malaria and typhoid fever with unknown medications. He took these medications for 45 days—until within a few weeks of his departure to the United States.

On physical examination he was febrile (102° Fahrenheit), hypotensive (85/47), tachycardic (110 bpm,) and tachypneic (22 bpm). He appeared uncomfortable, and had abdominal tenderness in the epigastrium and right upper quadrant without hepatosplenomegaly. Laboratory analyses were significant for hyperbilirubinemia (total bilirubin 3.2, conjugated bilirubin 1.8) and slightly elevated liver enzymes (ALT 58 U/L, AST 50 U/L). His electrolytes, creatinine, and complete blood count were normal. Peripheral blood smear revealed ring and gametocyte forms, within slightly enlarged infected red blood cells, consistent with *Plasmodium vivax* infection (Figures **13b.1** and **13b.2**). The patient's parasitemia was low (0.3%) and he was treated with chloroquine for 3 days. He was subsequently treated with 14 days of primaquine after G6PD testing was found to be normal.

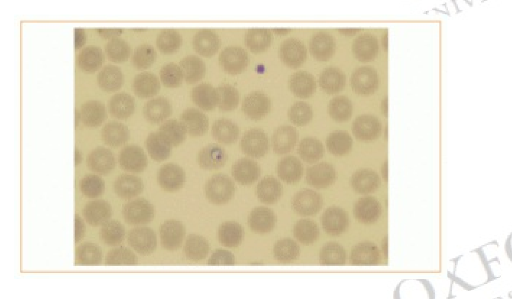


Figure 13b.1
Peripheral blood smear, Wright-Giemsa stain revealing an intraerythrocytic ring form.

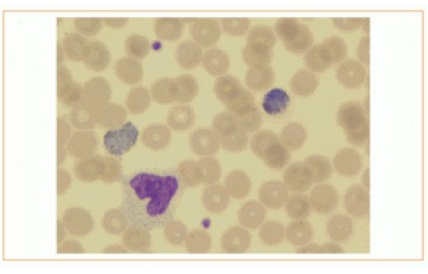




Figure 13b.2
Peripheral blood smear, Wright-Giemsa stain showing circulating gametocyte of *Plasmodium vivax*.

**Case 13b Discussion: *Plasmodium vivax* Malaria**

*Plasmodium vivax* is the most widespread of the four main *Plasmodium* species (*P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*) that infect humans, and occurs throughout most of the temperate zones and parts of the tropics. Non-*falciparum* malaria, predominantly *P. vivax*, accounts for 25%–40% of the global malaria burden, with between 132 and 391 million cases per year, though this may be an underestimation.[1] Of the total *P. vivax* cases reported outside Africa, ~60% occur in Southeast Asia and the Western Pacific. Within the South and Southeast Asian region, India contributes ~80% of the total cases.[2] *P. vivax* malaria (present in 1%–6% of the population in South and Southeast Asia) makes up the majority of cases in India.[2,3] For travelers, *P.falciparum* is more prevalent due to its overall greater transmission rate; only 15% of malaria cases in returning travelers are due to *P. vivax*.[4]

## Clinical Presentation and Diagnosis

Because it is rarely fatal, *P.vivax* does not receive the same attention as *P.falciparum*; however, *P. vivax* malaria is a morbid disease in endemic regions, and because it can remit and recur in up to 20%–80% of cases, it can lead to significant financial hardships due to work loss.[1] In most areas, the burden of disease is greatest in young children and infants, with immunity usually developing by 10 to 15 years of age. Differences in parasite virulence, host susceptibility, age of exposure, as well as parasite factors such as antimalarial drug resistance, may play a crucial role in the clinical presentation.[1]

Most often, patients present with fever, but it is rarely the classic tertian fever (every 48 hours) caused by synchronous schizont rupture. High fever and rigors are more common with *P. vivax* than with *P. falciparum* malaria, though *P. vivax* is capable of inducing fever at lower levels of parasitemia than *P. falciparum*, possibly secondary to greater induction of proinflammatory cytokines such as TNF-a. Pregnant women with *P. vivax* malaria may give birth to children with lower birth weight. Patients may present with severe anemia, respiratory distress, and coma, though *P. vivax* is rarely fatal and usually only causes death due to splenic rupture (Figure **13b.3**). Cerebral edema, renal failure, and placental malaria, as seen in *P. falciparum* infection, do not occur in *P. vivax* infections, due to low levels of parasite cytoadherence in the postcapillary venules in the latter species.



Figure 13b.3
CT scan abdomen, axial view showing spontaneous splenic rupture in a patient with *Plasmodium ovale* malaria.

## Diagnosis

Thick and thin peripheral blood smear microscopy is the gold standard for malaria diagnosis and calculation of percent parasitemia. In cases of severe malaria (e.g., *P. falciparum*), follow-up smears are recommended to evaluate for decreases in parasitemia with treatment. While the BiNaxNow rapid diagnostic test is approved by the FDA for hospital and commercial laboratories, it cannot determine the *Plasmodium* species, and at low levels of parasitemia, it may lead to false negative results.

Together with *Plasmodium ovale*, *Plasmodium vivax* is one of the relapsing forms of malaria: hypnozoites within the liver may reactivate months or even years after a patient has been treated for the erythrocytic forms. Both species tend to infect reticulocytes whose cytoskeletons are poorly developed and, therefore, infected cells will often appear enlarged on the peripheral blood smear. *P. falciparum* infects red cells of any age, and thus leads to higher levels of parasitemia. *P. falciparum* is also typified by multiply infected cells, appliqué forms, and “banana-shaped” gametocytes (Figures **13b.4** and **13b.5**). While it is possible to find schizonts of *P. vivax* and *P. ovale* on the peripheral blood smear, those of *P. falciparum* are usually attached to the endovascular tissue of small capillaries, and are rarely seen on the peripheral blood smear. *P. malariae* and *P. knowelsi* are similar in appearance on peripheral blood smear, and are characterized by the presence of band forms.[5]

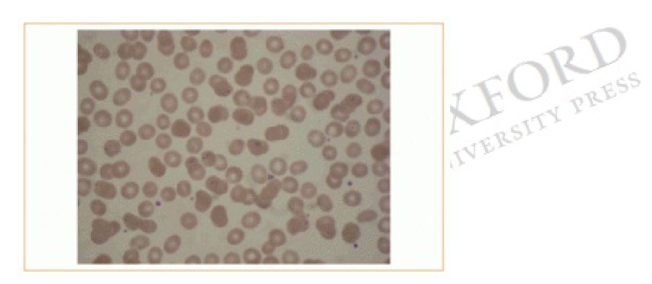




Figure 13b.4
Peripheral blood smear, Wright-Giemsa stain of a patient with *Plasmodium falciparum* malaria.

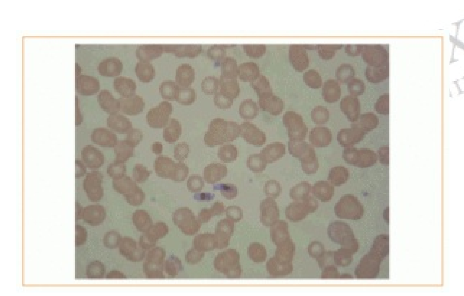




Figure 13b.5
Peripheral blood smear, Wright-Giemsa stain showing the banana-shaped gametocytes of *Plasmodium falciparum*.

## Treatment

Chloroquine is the mainstay of treatment for acute *P. vivax* malaria, and is usually given in 3–4 doses over the course of 2–3 days (600 mg base orally immediately, followed by 300 mg base PO at 6, 24, and 48 hours). Hydroxychloroquine is an alternative regimen (620 mg base PO immediately, followed by 310 mg base PO at 6, 24, and 48 hours). Plasma concentrations of chloroquine are sustained above the minimum inhibition concentration for at least 28 days, and thus are capable of suppressing the first relapse, which in tropical zones generally occurs at approximately 21 days. In chloroquine-resistant areas (Papua New Guinea and Indonesia), quinine sulfate in combination with doxycycline or tetracycline, or mefloquine or atovaquone-proguanil can be used.[6]

The previously mentioned antimalarials are active against erythrocytic forms, but have no activity against the dormant liver hypnozoites. In order to prevent further relapses, primaquine is used eliminate the hypnozoite forms. The standard recommendation has been 30 mg of primaquine daily over 14 days. Primaquine resistance is now reported in Papua New Guinea and Indonesia, and higher doses or longer courses have been advocated for patients returning from these areas.[1] Patients should be evaluated for G6PD deficiency prior to prescribing primaquine, since it may induce hemolytic anemia in these patients. Prevalence of the deficiency correlates with the geographic distribution of malaria, which has led to the theory that carriers of G6PD deficiency may have partial protection against malarial infection.[7] If G6PD deficiency is present, lower doses of primaquine are used and close monitoring for hemolytic anemia is recommended.

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## A 51-Year-Old Woman with Fever, Rash, and an Eschar

**Chapter:** A 51-Year-Old Woman with Fever, Rash, and an Eschar
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 51-year-old woman presented with 5 days of rash and fever. A day before her symptoms started, she noticed a small papule on her left calf that quickly became a blister, and then spontaneously opened and became black and adherent. By the next day, she developed papulovesicular rash on her face that spread over the next 2 days to her trunk and extremities. Her rash was not pruritic, but the lesion on her leg was mildly painful. She also developed fatigue, fevers (103°F), and chills that worsened over the course of the next few days. Her past medical history included poorly controlled type 2 diabetes mellitus and hypertension, for which she was taking insulin, metformin, atenolol, fosinopril, and aspirin. She immigrated to the United States from Colombia 20 years before presentation, and had always lived in the neighborhood of Jackson Heights, borough of Queens, in New York City.

She was employed as a commercial cleaner, working in different buildings across the city, where she occasionally saw mice. On physical examination, she was in no acute distress, and her vital signs were remarkable for elevated blood pressure (158/94 mm Hg) and low-grade fever (100.1°F). Several small, rubbery, mobile, tender lymph nodes were palpable in the submandibular, supraclavicular, and left inguinal regions. The diffuse papular rash involved her scalp, face, trunk, and extremities, but spared her palms and soles (Figures **13c.1 and 13c.2**). Some of the lesions had a clear central vesicle, and there was a 5mm × 5mm tender black eschar on her left calf that had surrounding erythema, but had no purulence (Figure **13c.3**). The rest of her physical examination was unremarkable.





Figure 13c.1 and 13c.2
Diffuse papular rash involving scalp, face, trunk and extremities.





Figure 13c.3
Black eschar on the left with surrounding erythema.

Other than mild leukopenia ($4.8 \times 10^3$ WBC/ul), laboratory studies and a chest radiograph were unrevealing, and she was treated with doxycycline 100 mg twice a day with resolution of the fevers within 24 hours and quick resolution of the rash. Acute serology for *Rickettsia ricketsii*, *Rickettsia typhi* and *Rickettsia akari* were all negative, but convalescent *Rickettsia akari* antibodies 8 weeks later were positive.[1] (p. 256)

**Case 13c Discussion: Rickettsialpox**

## Clinical Features and Diagnosis

Rickettsialpox is a zoonotic illness caused by the obligate intracellular Gram-negative coccobacillary bacteria, *Rickettsia akari*. It was identified in Kew Gardens, borough of Queens, New York City, in 1946 by Dr. Benjamin Shankman, and initially named "Shankman's disease." It was later renamed "Kew Gardens spotted fever," only to have its name changed again later to rickettsialpox. The infection is transmitted to humans via a mite vector (*Lyponyssoides sanguineus*; Figure **13c.4**), which feeds on the asymptomatic reservoir host, the common house mouse (*Mus musculus*). While most cases of rickettsialpox have been reported from the East Coast of the United States (New York, Connecticut, Maryland, Massachusetts, Ohio, Pennsylvania and North Carolina), there have been cases described in Arizona and Utah, as well as Mexico, Turkey, South Africa, Croatia, Ukraine and Korea.[2]

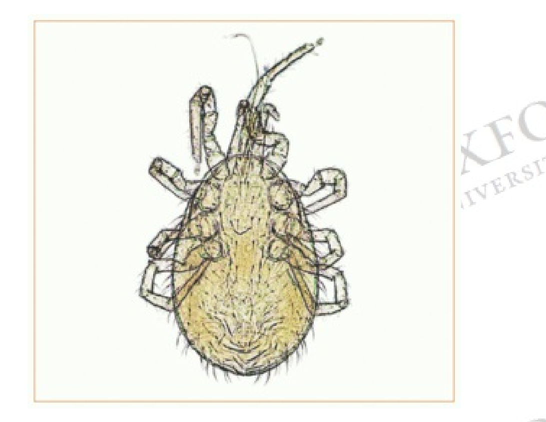




Figure 13c.4
The mite vector of Rickettsialpox, *Lyponyssoides sanguineus*. Adapted from Saini R, Pui JC, Burgin S. *J Am Acad Dermatol*. 2004 Nov;51(5 Suppl):S137–42.

Rickettsialpox begins with a bite of an infected mite, which forms a black eschar at the site of inoculation. Three to seven days after the appearance of the primary lesion, infected patients may develop fever and a papulovesicular rash that spares palms and soles. Headache (reported in 90%–95% of the cases) is a very common symptom, and other symptoms such as myalgias, arthralgias, back pain, sore throat, and gastrointestinal complaints are present in 30% of the cases. The rash is present in approximately 22% of the cases, and regional lymphadenopathy at the draining site of the eschar has been reported in 17% of the cases. Generalized lymphadenopathy, which was commonly reported with the first case descriptions of the disease, was found to be uncommon in a more recent case series.[1] The number of papulovesicular lesions is highly variable, having been described from 5 or 6 to as much as a 100; on average, patients develop between 20 and 40 lesions.[2]

Laboratory findings are usually nonspecific. About a third of the patients develop a mild leukopenia with lymphocytic predominance, and cases of acute hepatitis caused by rickettsialpox have been reported.[3] Because of the delay of the available methods in providing a rapid diagnostic confirmation, the diagnosis of rickettsialpox often relies on the clinical triad of eschar, rash, and fever. Since a myriad of conditions can mimic this disease, it is important to initiate a proper diagnostic evaluation as soon as rickettsialpox is suspected—usually, with paired serum samples for antibody testing. Acute phase antibodies to *R. akari* by indirect immunofluorescence (IFA) are positive (20% of the time in confirmed cases.[2] An elevated IgM to *R. akari* is typically indicative of acute infection, but an elevated IgG may be due to current or past infection.[4] Convalescent antibodies are obtained 3–4 weeks after the acute sample (6–8 weeks if the patient was treated with doxycycline) and, if increased fourfold from baseline, are diagnostic of rickettsialpox infection.

Patients with *R. akari* infection often have antibodies that cross-react with other spotted fever group antibodies; their antibodies to *R. rickettsii* may be positive, although typically at a lower titer. Immunohistochemical staining (IHC) of paraffin-embedded skin biopsy specimens is a highly sensitive technique for confirming the diagnosis. In a study that included 18 patients with laboratory-confirmed rickettsialpox, 16/16 (100%) patients who had an eschar biopsy and 5/9 (55%) who had a papulovesicular lesion biopsy had a positive result.[1] *R. akari* has also been successfully cultured from fresh eschar biopsies of 5/7 (71%) patients with IHC-confirmed rickettsialpox.[5] While *R. rickettsii* antibodies can be obtained in commercial laboratories, *R. akari* IFA and IHC can only be obtained through the Centers for Disease Control and Prevention (CDC) in the United States. *R. akari* culture remains investigational only.

The differential diagnosis of rickettsialpox includes chickenpox, herpes simplex, and brown recluse spider bite, among others. Cutaneous anthrax should always be considered when evaluating a patient with a fever and an eschar. The eschar from anthrax, however, tends to be painless and associated with more edema.[1] In patients with the appropriate geographic background, other spotted fever group rickettsial infections need to be considered. Patients with Rocky Mountain spotted fever tend to be more acutely ill, do not present with an eschar, and have a rash that involves the palms and soles.

Returned travelers from southern Africa may present with a similar illness, including a black eschar ("tache noire") at the site of inoculation of the bacteria (Figure **13c.5**). These organisms infect local endothelial cells in the skin, and the resulting ischemia causes tissue necrosis. African tick-bite fever is caused by *R. africae,* and is transmitted by *Amblyomma* ticks. Another rickettsial disease, Mediterranean spotted fever (also known as Boutonneuse fever) is endemic in the Mediterranean coast of Europe, northern Africa, and South Africa. It presents with an eschar, fever, and a maculopapular rash that often involves palms and soles. The causative agent, *R. conorii* is transmitted by the tick *Ripichephalus sanguineus.*[2]






Figure 13c.5
*Tache noire* in a patient with African tick-bite fever.

## Treatment

Rickettsialpox is a self-limited disease, and without treatment, it usually resolves within 7 to 10 days. Relapses and reinfections have not been reported, making it possible that immunity in humans is complete and lifelong. Doxycycline 100 mg twice daily for 5 to 7 days is highly effective, and the fever and rash typically resolve within 24 to 48 hours after initiation of treatment. Chloramphenicol has also proven effective, but it is generally avoided because of potential toxicity.[2]

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A Call from the Hematology Lab

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**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

An 82-year-old man presented to the emergency room with nausea, vomiting, and diarrhea. He also reported intermittent fevers and chills, along with drenching night sweats that required his daughter to change his bedclothes at night for the past 2 months. His past medical history was significant for diabetes mellitus complicated by retinopathy, hypertension, hyperlipidemia, coronary artery disease, pacemaker placement for heart block, gout, gastritis and hepatitis C. He had been hospitalized at an outside institution 2 months prior to admission for gastrointestinal bleeding, and had been transfused 3 units of packed red blood cells. He was originally from Puerto Rico, but lived with his daughter in an apartment in East Harlem for many years and had not recently traveled.

On physical examination, he was an elderly, thin, blind man who was afebrile at the time of presentation with a normal heart rate (90 beats per minute) and blood pressure (120/61 mm/Hg). He had scleral icterus but no hepatosplenomegaly, and the remainder of his physical examination was unremarkable. Laboratory examination was significant for leukocytosis (15 × $10^3$ WBC/μl, 72% neutrophils), anemia (hemoglobin 7.4 g/dl), thrombocytopenia (120 × $10^3$ platelets/μl) and acute renal insufficiency (creatinine 2.5 mg/dl). He had signs of hemolysis with elevated total and direct bilirubin (6.9 mg/dl and 4.6 mg/dl, respectively), LDH (837 U/L), and reticulocyte count (10.4%), and low haptoglobin ((6 mg/dl).

A technologist from the hematology lab noted parasites on a routine peripheral blood smear: intraerythrocytic ring forms were seen along with tetrads of intracellular merozoites consistent with the diagnosis of babesiosis (Figures **13d.1** and **13d.2**). He was treated with atovaquone and a macrolide. *Babesia microti* serology confirmed the diagnosis (IgG ) 1:256, IgM 1:80; *Babesia* PCR positive). Given his lack of travel and exposure to the outdoors, an investigation was conducted regarding the blood donors from whom he had received the transfusions. One of the three donors was found to have positive *Babesia* serology.

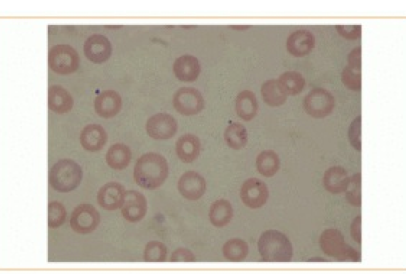




Figure 13d.1
Peripheral blood smear, Wright-Giemsa stain with intraerythrocytic ring forms of *Babesia microti*.

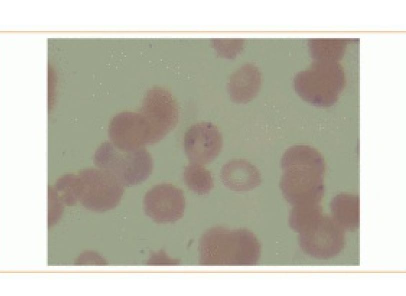



Figure 13d.2
Peripheral blood smear, Wright-Giemsa stain showing tetrads of intracellular merozoites.

**Case 13d Discussion: Babesiosis**

Human babesiosis is a tick-borne illness caused by protozoa of the genus *Babesia,* which are obligate parasites of red blood cells. Historically, the first account of babesiosis is theorized to occur in the Old Testament, Exodus 9:3, which describes a plague visited upon the cattle of Pharaoh Rameses II. Later, Victor Babes, a Hungarian pathologist, first described the microorganism when investigating the cause of a febrile hemoglobinuria in cattle. Subsequently, Smith and Kilbourne found a similar organism that infected Texas cattle, and identified that the parasite was transmitted by a cattle tick; this was the first observation that an arthropod could transmit an infectious agent to a vertebrate host. The first human case of babesiosis was not identified until 1957 when a young asplenic farmer near Croatia, who had been grazing cattle, died of an illness in which he presented with fever, anemia, and hemoglobinuria. Around the same time, residents of Nantucket Island were presenting with a febrile illness dubbed "Nantucket fever."[1]

The epidemiology of human babesiosis has changed over the past 50 years with an increasing number of cases being diagnosed. While there are over a 100 species of *Babesia* identified, *Babesia microti* is the most common cause of human babesiosis in the United States. Endemic areas initially included Nantucket Island, Martha's Vineyard, Cape Cod, Block Island (RI), eastern Long Island, Shelter Island, and Fire Island. This has now expanded to include large portions of the mainland that extend from Rhode Island and Connecticut down to New York and New Jersey. More recently, a new species of *Babesia* termed WA-1 or *B. duncani* has been reported to cause human cases in Washington State and northern California. In Europe, the majority of cases are due to *B. divergens* which can cause a more severe infection, especially in asplenic individuals. A similar species to *B. divergens* has also been reported in Missouri and Wisconsin.[2]

The life cycle of *Babesia* is complex and involves asexual budding in erythrocytes in the mammalian host, and sexual reproduction in the arthropod vector (Figure **13d.3**). Maintenance of the *Babesia* species is dependent on the presence of both these hosts. The life cycle of *Babesia microti* is the most well-described. The primary tick vector is *Ixodes scapularis,* well-known because it is also the vector for *Borrelia burgdorferi* and *Anaplasma phagocytophilum,* the causative agents of Lyme disease and human granulocytic anaplasmosis. The primary reservoir in the northeastern United States is the white-footed mouse, or *Peromyscus leucopus*. The white-tailed deer also serves as an important host for maintenance and transport of the ticks, although it is not a primary reservoir for *B. microti.* The growth of the deer population over the last few decades may be a contributing factor for the increase in number of *Babesia* cases.[2]

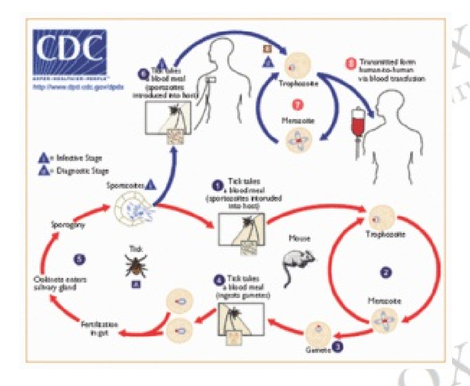
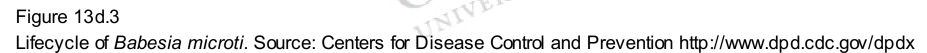
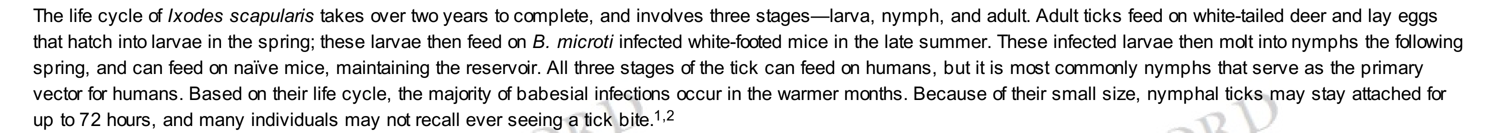



Figure 13d.3

Lifecycle of *Babesia microti*. Source: Centers for Disease Control and Prevention http://www.dpd.cdc.gov/dpdx


The life cycle of *Ixodes scapularis* takes over two years to complete, and involves three stages—larva, nymph, and adult. Adult ticks feed on white-tailed deer and lay eggs that hatch into larvae in the spring; these larvae then feed on *B. microti* infected white-footed mice in the late summer. These infected larvae then molt into nymphs the following spring, and can feed on naïve mice, maintaining the reservoir. All three stages of the tick can feed on humans, but it is most commonly nymphs that serve as the primary vector for humans. Based on their life cycle, the majority of babesial infections occur in the warmer months. Because of their small size, nymphal ticks may stay attached for up to 72 hours, and many individuals may not recall ever seeing a tick bite.[1,2]

After attachment of a tick, *B. microti* infected erythrocytes accumulate in the gut of the insect and fuse to form an ookinete that invades the tick salivary glands. The ookinete transforms into dormant sporoblasts until the next stage of the tick (nymph or adult) takes a blood meal from a vertebrate host. The sporoblasts are activated and liberate up to 10,000 sporozoites into the skin of the host, and then invade erythrocytes. Once inside the cytoplasm, the organism is visible as a ring-shaped trophozoite that reproduces by budding in two planes. The resultant four merozoites form the tetrad most commonly described as the "Maltese cross"—pathognomonic for *Babesia* infection. Lysis of the red blood cells than occurs followed by release of merozoites and infection of other red blood cells.[1,2]

Clinical manifestations of babesiosis may range from asymptomatic infection to severe, fulminant illness. Incubation time varies but symptoms usually appear one to six weeks after the initial tick bite. The majority of humans infected with *B. microti* will experience a mild flu-like illness, including fevers, chills, malaise, headache, anorexia, and myalgias. Other less common symptoms include cough, sore throat, dyspnea, nausea, vomiting, and diarrhea; some patients may even experience emotional lability, mild depression, and hyperesthesia. Healthy individuals may remain completely asymptomatic from babesial infection for months or years, and may serve as a source of transfusion-transmitted babesiosis.[2]

Findings on physical examination may include fever, splenomegaly, and hepatomegaly. Rash is unusual, and is usually indicative of concurrent Lyme disease. Laboratory abnormalities may include hemolytic anemia (Coombs test may be positive), elevated liver enzymes, and thrombocytopenia. Urinalysis is usually notable for hemoglobinuria or proteinuria. Parasitemia levels are 1%–20% in the majority of patients; however, in asplenic patients, parasitemia levels can be as high as 85%. Severe illness is usually seen in asplenic individuals, elderly patients, and immunocompromised hosts, including those coinfected with HIV. Complications of babesiosis include acute respiratory distress syndrome, disseminated intravascular coagulation, and congestive heart failure. Renal failure, hepatic failure, and myocardial infarction have also been described. In patients who are hospitalized, mortality may be as high as 5%–9%.[1]

The diagnosis of babesiosis can be challenging because the symptoms are often nonspecific. Babesiosis is usually detected on Giemsa or Wright stained thick and thin peripheral blood smears. *Babesia microti* may be difficult to differentiate from *Plasmodium falciparum* on peripheral blood smear, as both have intraerythrocytic ring forms; however, extraerythrocytic forms and the presence of tetrads of merozoites are distinguishing features of *Babesia* infections. Multiple blood smears over the course of several days may need to be examined in cases of low parasitemia. Confirmatory *Babesia* PCR is highly sensitive and specific, but the delay in obtaining results limits its clinical usefulness. Serology using an indirect immunofluorescent antibody (IFA) may also be used for confirmation. A serum IgG titer of 1:64 is diagnostic, and a titer greater than 1:1024 may indicate active infection. Antibody titers usually return to 1:64 or less, 8 to 12 months after infection.[1,2]

Symptomatic individuals with babesiosis should be treated. In individuals with severe disease, a combination of intravenous clindamycin and oral quinine should be given for

7 to 10 days. Partial or complete red blood cell exchange transfusion has been used as an adjunctive therapy in cases of severe disease with high parasitemia. In individuals with mild to moderate disease, an alternative regimen of atovaquone plus a macrolide may be used for 7–10 days. This combination was found to be as effective as clindamycin and oral quinine in a prospective, nonblinded, randomized trial of 58 patients with non-life-threatening babesiosis. There was no significant difference in duration of parasitemia, but adverse reactions were significantly higher in the group treated with clindamycin and quinine.[3]

As described in the case above, babesiosis can be transmitted through blood transfusion and recent reports suggest that the number of fatalities from transfusion-transmitted babesiosis is increasing.[4] Currently, only individuals with a history of babesiosis are prohibited from donating blood and PCR screening of blood for *Babesia* is not yet FDA-approved. As many individuals remain asymptomatic with babesiosis for months to years and never recall a tick bite, a potential blood donor may remain infectious for extended periods. In addition, *Babesia microti* can survive refrigerated conditions used for blood storage for 21–35 days.[5] Given these factors, physicians should have a high clinical suspicion for babesiosis when patients present with a febrile illness and hemolytic anemia after recent blood transfusion.

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## Altered Mental Status, Thrombocytopenia and Leukopenia in a Hiker

**Chapter:** Altered Mental Status, Thrombocytopenia and Leukopenia in a Hiker
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Clinical Presentation and History

A 71-year-old woman presented to the emergency room in early July with weakness and fatigue. She reported that the fatigue had begun two days prior, and had been associated with nausea, vomiting, and diarrhea. She had also experienced several episodes of shaking chills and near syncope, and had been unable to get out of bed for the 24 hours prior to admission. The patient's medical history included diabetes, hypertension, and hyperlipidemia managed with nateglinide, valsartan, and simvastatin. In the emergency department, she noted increased thirst and abdominal pain, but denied fevers, rash, myalgias, arthralgias, headache, or dysuria. Her daughter reported that she had been slightly confused in the 24 hours before admission. She was an avid hiker and member of a hiking club; her last hike had been almost 2 weeks prior on Bear Mountain in upstate New York. She was originally from China, and 3 months before her presentation she had been hiking in the mountains of Peru.

On physical examination, the patient was febrile (39.6° Celsius) and tachypneic (24 breaths per minute) though her heart rate (64 beats per minute) and blood pressure (109/62) were normal. She was lethargic but arousable, and unable to recall the details of recent events. She had dry mucous membranes and faint rales in the bases of both lungs, but the remainder of her physical exam was unremarkable. Laboratory values on admission were notable for leukopenia ($2.8 \times 10^3$ WBC/μl, 84% neutrophils), thrombocytopenia ($19 \times 10^3$ platelets/μl), and elevated liver enzymes (AST 294 U/L, ALT 114 U/L, LDH 856 U/L). She was also hyperglycemic (295 mg/dl), but the remainder of her laboratory studies including hemoglobin (14.9 g/dl), creatinine (0.9), alkaline phosphatase (64 U/L), and GGT(36 U/L) were normal. Her chest radiograph revealed small bilateral pleural effusions. Her peripheral blood smear and buffy coat smear were notable for neutrophils with intracytoplasmic morulae (Figures **13e.1** and **13e.2**), and intravenous doxycycline was initiated.

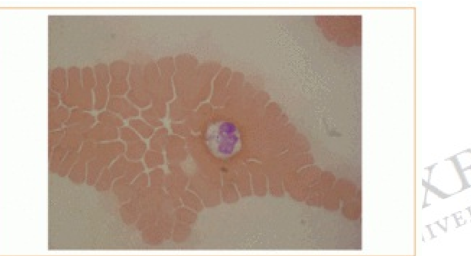




Figure 13e.1
Peripheral blood smear, Wright-Giemsa stain showing neutrophils with intracytoplasmic morulae.

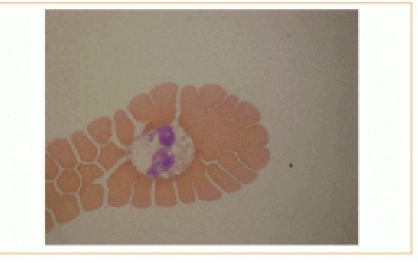






Figure 13e.2
Peripheral blood smear, Wright-Giemsa stain showing neutrophils with intracytoplasmic morulae.

The patient's mental status worsened on the day after admission; she was increasingly tachypneic, and was transferred to the intensive care unit. Her leukopenia and thrombocytopenia worsened (1.3 × $10^3$ WBC/µl, 15 × $10^3$ platelets/µl), and markers of liver inflammation and cellular destruction peaked on day four (AST 1205 U/L, ALT 404 U/L, LDH 2461 U/L), but by this time she began to improve clinically, with return of her normal mental status. One week after her admission she was discharged home, and her subsequent complete blood counts and liver enzymes were normal. Her acute serum titer for human monocytic ehrlichiosis (HME) was negative, but the human granulocytic anaplasmosis (HGA) serology was not resulted (insufficient quantity was sent to the lab for testing). Three months later, the patient's HGA IgM was negative but the HGA IgG was positive (1:512). Serology for Lyme disease was negative and no intraerythrocytic parasites were seen on examination of the peripheral blood smear. The patient returned to hiking and was advised to use DEET-based skin repellents, long-sleeved clothing, and premethrin clothing treatments for tick-bite prevention.

**Case 13e Discussion: Human Granulocytic Anaplasmosis**

## Microbiology and Taxonomy

Human ehrlichiosis encompasses five different obligate intracellular bacteria of the Anaplasmataceae family, three of which have been extensively described in the literature to cause human disease.[1] Human monocytic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis* and targets mainly monocytes. The vector for this organism is the lone star tick (*Amblyomma americanum*; Figure **13e.3**), and the animal reservoir is the white-tail deer.[2] Most infections occur between May and July, and the regions with the highest prevalence include the southeastern, south central, and mid-Atlantic United States.[2]



Figure 13e.3
The lone star tick (*Amblyomma americanum*), vector of *Ehrlichia chaffeensis*.

Human granulocytic anaplasmosis (HGA) is caused by *Anaplasma phagocytophilum,* and principally targets granulocytes. The vectors for this organism in North America are the ticks *Ixodes scapularis* (Figure **13e.4** and **13e.5**; in the northeastern and upper Midwestern United States) and *Ixodes pacificus* (in the western United States).[3] *Ixodes scapularis* is also the vector for *Borrelia burgdorferi*, the agent of Lyme disease, and *Babesia microti,* the agent of babesiosis. Since simultaneous infections can occur in a single patient, the diagnosis of one infection transmitted by *I. scapularis* should prompt evaluation for the other two. Other animals that serve as reservoirs include white-tailed deer and white-footed mice, among other small rodents.[3] *Ehrlichia ewingii* is a canine pathogen now known to cause infections in humans, referred to as *Human ewingii ehrlichiosis*; this organism also targets neutrophils.[1]

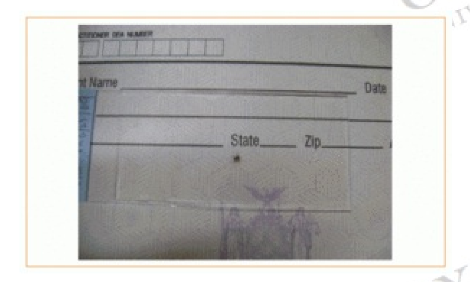





Figure 13e.4
Ixodes scapularis, the vector of *Anaplasma phagocytophilum*.





Figure 13e.5
Ixodes scapularis, the vector of *Anaplasma phagocytophilum*.

Infections with human ehrlichiosis are nationally reportable illnesses in the United States, and prevalence data demonstrate that the number of cases is steadily increasing, with over 4000 cases of HGA since 1994[3] and over 2000 cases of HME since 1986.[1] Surveillance studies of serum titers for these infections suggest evidence of infection in endemic areas of greater than 10%, suggesting the case reporting is an underestimation of true incidence of these diseases.[1]

## Clinical Features and Diagnosis

The clinical presentation of all types of human ehrlichiosis is characterized by similar symptoms and laboratory findings. Most patients report fever, headache and malaise. Confusion occurs in about 20% of patients, and nausea, vomiting, and diarrhea are also common.[1] Laboratory studies are notable for leukopenia, thrombocytopenia, and elevated transaminases in the majority of cases.[1] Human monocytic ehrlichiosis is associated with the development of more severe illness (including shock) and higher mortality than patients with HGA. Immunocompromised hosts are at especially higher risk for complicated HME.[1]

The most rapid diagnostic test is evaluation of the buffy coat or peripheral blood smear, for the presence of intracytoplasmic morulae (Latin for *mulberry*) in monocytes or neutrophils. The buffy coat is the fraction of centrifuged blood with the highest concentration of white cells, and examination of this fraction makes identification of clusters of intracellular bacteria more likely than examination of the peripheral blood smear alone. Sensitivity is highest during the first week of infection, and higher in HGA than HME.[1] Alternative methods of diagnosis include PCR and serology. The sensitivity of PCR ranges from 60%–90%,[1] but is not widely available. Serologic testing is more commonly used; diagnosis is based on the detection of seroconversion or a fourfold change in antibody titer during the convalescent phase. The sensitivity of serologic testing is high: 88%–90% for HME and 82%–100% HGA.1 Culture of the causative organisms is extremely difficult, usually requiring 2–6 weeks of incubation and a specialized laboratory.[1]

## Treatment

The literature on treatment of human ehrlichiosis is limited but, based on clinical experience and cell culture, this group of infections is susceptible to the tetracyclines. Doxycycline is the drug of choice, and patients generally improved rapidly, within 24–48 hours of treatment initiation. For pregnant patients and children, rifamycins have been used successfully. A retrospective cohort study evaluating timing of initiating therapy found that delayed administration of doxycycline (beyond 24 hours following admission) resulted in significantly more complications.[4] These complications included respiratory failure, prolonged duration of illness, prolonged hospitalization, and intensive care unit stay.[4] Thus, if the diagnosis of human ehrlichiosis is suspected, therapy should be initiated promptly before results of confirmatory diagnostic testing are available.

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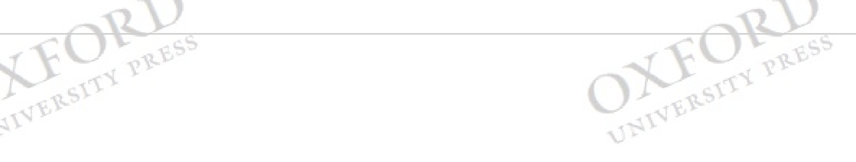






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## Prolonged Postpartum Fever

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**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 25-year-old female with no significant medical history was admit-ted for a complicated delivery of twins. The first twin was delivered vagi-nally after a preterm premature rupture of membranes. The second twin was delivered via cesarean section 21 days later. Shortly after delivery, the patient became febrile and developed diffuse abdominal pain. She was treated for 5 days with clindamycin, gentamicin, and ampicillin for presumed endometritis, but her fevers persisted.

On physical examination, the patient was febrile but hemodynamically stable. She had diffuse abdominal tenderness with voluntary guarding. Her incision site was nontender and had no erythema or discharge. Her laboratory studies were notable for a leukocytosis of $22 \times 10^3$ WBC/μl, but her blood cultures and chest radiograph were negative.

#### Differential Diagnosis and Hospital Course

In the setting of a complicated peripartum course culminating in a cesarean section, endometritis was initially very high on the differential, so the patient was treated empirically with antibiotics. The diagnosis of endometritis is often made clinically when a postpartum patient has fever and uterine tenderness, as laboratory data are nonspecific, blood cultures are often negative, and endometrial cultures are difficult to collect without con-tamination from the lower genital tract. Patients are often started empirically on a standard triple antibiotic regimen including clindamycin, gentamicin, and ampicillin, to cover mixed aerobic and anaerobic pathogens. This regimen has a success rate of nearly 90%, and most patients' fevers resolve within 24–48 hrs.[1] As in this case, if the patient fails to defervesce on this regimen, alternative diagnoses should be explored. Postoperative complications, such as a surgical site infection or thrombosis, were also on the differential, so a CT scan of the abdomen and pelvis was recommended (Figure **14a.1**).

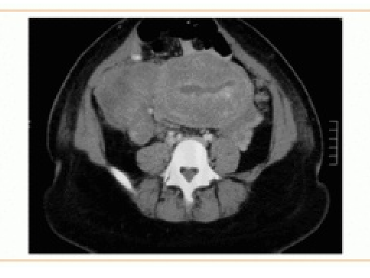




Figure 14a.1
CT scan pelvis, axial view showing dilatation of the right ovarian vein with a thrombus extending into the inferior vena cava.

The CT scan showed dilatation of the right ovarian vein with a thrombus extending into the inferior vena cava. The patient was continued on antibiotics and was started on anticoagulation with heparin. Her fevers resolved over the next 48 hours and antibiotics were discontinued.

#### Case 14a Discussion: Septic Pelvic Thrombophlebitis

Septic pelvic thrombophlebitis is divided into two entities: postpartum ovarian vein thrombosis (POVT), and deep septic pelvic thrombophle-bitis (DSPT), also known as enigmatic fever. The entities often occur together, and share the same pathogenic mechanism, but differ in clinical presentation and diagnostic findings. POVT presents within the first week postpartum as fever and abdominal pain refractory to antibiotics, and a thrombosis of the ovarian vein is seen on imaging. DSPT presents as an unlocalized postpartum fever with no radiographic evidence of thrombosis. The remainder of this discussion will focus on POVT. These thrombotic complications occur in 1 in 3000 deliveries—one in 9000 vaginal deliveries, and one in 800 cesarean deliveries.[2] Vircow's triad (endothelial damage, hypercoagulability, and venous stasis) is represented in the pathogenesis of POVT. Endothelial damage occurs from trauma during delivery, or from preceding infection with endometritis. A clinical diagnosis of endometritis often precedes that of POVT, and cultures from thrombi yield microorganisms commonly found in endometritis.[2] In addition, pregnancy is a hypercoagulable state, as many of the clotting factors are upregulated, and there is a decrease in fibrinolysis that occurs in the immediate postpartum period. Lastly, venous stasis occurs in pregnancy due to

dilatation of the ovarian veins that is accompanied by low velocity flow. This leads to retrograde (left to right) ovarian venous flow, which, along with the dextrotorsion of the enlarged uterus that causes compression of the right ovarian vein, explains why POVT occurs on the right side in 90% of cases.[2]

POVT presents as fever and abdominal pain within one week post-partum, which does not respond to at least 5 days of appropriate antibiotics. The incidence peaks at postpartum day 2, but 90% of patients will present within 10 days postpartum.[3] Patients appear clinically ill, often with abdominal pain over the affected vein that may radiate to the groin or upper abdomen. Patients can present with a tender, rope-like abdominal mass that represents the thrombosed vessel; this physical sign is diagnostic of POVT but is seen in less than 50% of cases. Less than 2% of cases present as pulmonary emboli, but they tend to be small and rarely cause hypoxia.[3] The diagnosis of POVT is often made clinically, and when it is suspected, imaging is necessary to confirm the diagnosis and to guide treatment. CT is the modality of choice, and has a sensitivity of over 90% in detecting a thrombus.[3]

The treatment of POVT includes antibiotics and anticoagulation; surgical treatment using pelvic vein ligation is rarely considered for failure of medical therapy. The antibiotics used for POVT mirror those for endometritis, as infection often precedes thrombosis. The regimen, known as the triple antibiotic regimen, includes clindamycin, gentamicin in once daily dosing, and ampicillin. Other single agent antibiotic regimens, including ampicillin-sulbactam, ticarcillin-clavulanic acid, piperacillin-tazobactam, or third-generation cephalosporins, were found to be noninferior to the triple antibiotic regimen in individual studies of endometritis. When synthesizing the data in a meta-analysis, however, the triple antibiotic regimen was found to have fewer treatment failures and wound infections when compared to other single agent antibiotic regimens.[1]

Antibiotics are necessary but not sufficient in the treatment POVT, as the clinical definition of POVT is persistent fever despite antibiotics. In the 1970s, it was noted in several small case series that the addition of heparin to antibiotics in the treatment of presumed POVT led to rapid resolution of fever. The resolution of fever with anticoagulation actually became part of the criteria for diagnosing POVT; if the addition of heparin was followed by defervescence within 48–72 hours, this was considered pathognomonic for POVT. None of the data for anticoagulation were based on randomized, prospective trials, however. Moreover, the diagnosis of POVT was based on the response to heparin and was often not confirmed by laparotomy or radiology; patients may have defervesced over time, even without anticoagulation.

The utility of heparin was called into question by a prospective, randomized trial by Brown, et al. in 1999.[4] Women with postpartum fever despite 5 days of triple antibiotic therapy underwent CT scan, wherein 15 women were found to have POVT and were randomized to continue antibiotics alone or with heparin. The duration of fever and hospital stay were equivalent between the two groups. Moreover, no thromboembolic events, and no episodes of reinfection or postphlebitis syndrome, were reported for up to 3 months postpartum in either group. The authors concluded that there was no support for empiric heparin in postpartum women persistently febrile after 5 days of antibiotics. Only 20% of patients in their study were found to have a thrombus using modern imaging, and the majority of these patients became afebrile with another 3 days of antibiotics alone. This study is criticized for its small sample size, however, and was powered to assess for fever resolution only. It did not address the potential benefit of anticoagulation with regard to the risk of thrombus extension or pulmonary embolism. Thus, despite conflicting evidence about the efficacy of heparin, it is still considered part of the management of POVT.

Current recommendations, based on expert opinion, advocate for pelvic imaging in postpartum patients with persistent fever despite 5 days of appropriate antibiotics. If a thrombus is found on CT scan, heparin should be added to antibiotics and continued for 7–14 days after fever resolution. Antibiotics should be stopped within 48–72 hours after defervescence, and long-term anticoagulation with warfarin should only be considered if there is extensive thrombus extending into the renal veins or inferior vena cava. Some experts recommend repeating imaging 3 months following treatment, to demonstrate clot dissolution prior to stopping anticoagultion.[3] Recurrence is uncommon, and complications such as thrombus extension, septic pulmonary emboli leading to lung abscesses or empyema, endocarditis, ovarian abscess or infarction, or ureteral obstruction are extremely rare and have only been reported as case reports.

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## Worsening Dyspnea and Pulmonary Infiltrates

**Chapter:** Worsening Dyspnea and Pulmonary Infiltrates
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### Presentation and Case History

A 25-year-old woman with no past medical history presented with fever, chills, nonproductive cough, and dyspnea over the course of two weeks. She had been treated empirically with azithromycin followed by levofloxacin, but still had intermittent fevers as high as 102° F and precipitously worsening dyspnea. On physical examination, she was in mild respiratory distress, tachypneic (respiratory rate 34, saturation 87% on ambient air), tachycardic (heart rate 123 beats per minute), with slightly increased temperature (37.9 ° Celsius) and normal blood pressure (113/68). Coarse ronchi and bilateral wheezes were noted on pulmonary examination.

Laboratory values were significant for leukocytosis (32 × $10^3$ WBC/μl), thrombocytosis (647 × $10^3$ platelets/μl) and elevated lactate dehydrogenase (293 units/liter), and arterial blood gas analysis revealed hypoxemia and respiratory alkalosis (pH 7.52/$pCO_2$ 30/$pAO_2$ 60 mm Hg). Imaging of the lungs with plain radiography and CT angiography revealed bilateral alveolar in-filtrates and no evidence of pulmonary emboli (Figures **14b.1** and **14b.2**).

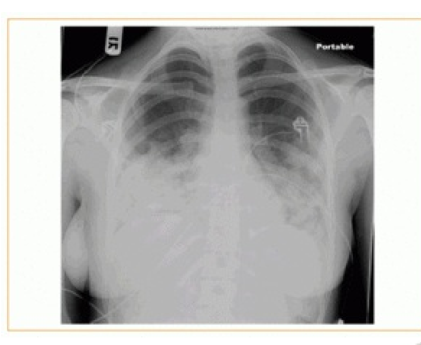






Figure 14b.1
Chest radiograph, anterior posterior view showing diffuse bilateral alveolar opacification

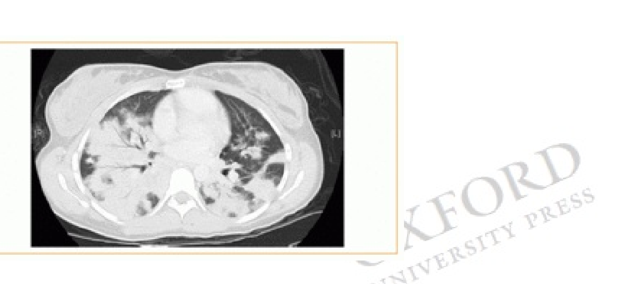




Figure 14b.2
Chest CT, axial view showing extensive bilateral alveolar infiltrates with air bronchograms.

She was empirically treated with vancomycin, cefepime, and azithromycin, and eventually underwent bronchoscopy because of persistent dyspnea. Immunologic evaluation including HIV testing and gamma globulin levels revealed no evidence of immunodeficiency. Blood, sputum, and bronchoalveolar lavage cultures were negative for bacteria, mycobacteria, fungi, and viruses, and *Legionella* urine antigen testing and direct fluorescence antibody testing were also negative. Histologic examination of the transbronchial

lung biopsy revealed chronic interstitial and focal organizing pneumonia, with no evidence of infectious organisms on acid-fast or fungal stains (Figure **14b.3**). Given the absence of inciting factors, such as a concomitant connective tissue disorder, malignancy, or medication exposure, and based on the histopathologic findings of the transbronchial lung biopsy, the diagnosis of cryptogenic organizing pneumonia (COP) was established. The patient was treated with oral prednisone and inhaled steroids, with resolution of her symptoms and pulmonary infiltrates. She had two subsequent relapses of dyspnea and cough that also responded to oral and inhaled steroids.

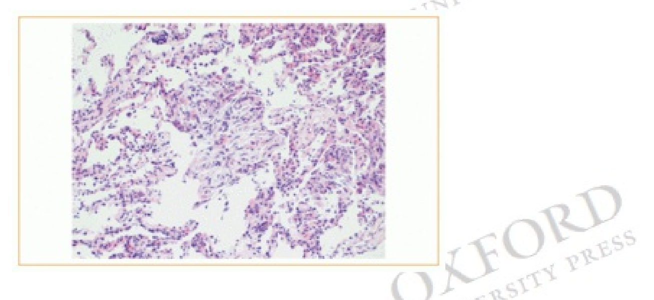


Figure 14b.3
Transbronchial biopsy, Hematoxylin and Eosin stain showing mild chronic inflammatory cell infiltrates within the alveolar septa and organizing pneumonia within an airspace.

**Case 14b Discussion: Cryptogenic Organizing Pneumonia**

## Clinical Presentation and Diagnosis

Cryptogenic organizing pneumonia was previously referred to as idiopathic bronchiolitis obliterans organizing pneumonia, or BOOP. This disorder is an idiopathic form of organizing pneumonia in which disease onset is usually within the fifth and sixth decades of life. There is no gender predilection, and cigarette smoking does not appear to be a predisposing factor. Clinical features initially may be difficult to distinguish from community-acquired pneumonia—a subacute, flu-like illness is followed by nonproductive cough, dyspnea on exertion, and weight loss. The majority of patients with COP have a period of 3 months of symptoms before the diagnosis is confirmed, highlighting the subacute nature of this disease.[1]

Laboratory studies are usually nonspecific, but it is noteworthy that a significant portion of COP patients have some degree of leukocytosis, and most have markedly elevated C-reactive protein levels and erythrocyte sedimentation rates. On plain radiographs of the chest bilateral, diffuse alveolar opacities in the presence of normal lung volumes may be seen. Computed tomography of the chest usually reveals more extensive disease, with patchy air-space consolidation and ground-glass opacities (frequently in the periphery of the lung and in the lower lung zones) being most common. Small nodular opacities, bronchial wall thickening, and dilation also occur. Pulmonary function tests commonly show mild to moderate restriction, and abnormal gas exchange patterns with reduced diffusion capacity (DLCO) and resting hypoxemia are usually present. Bronchoalveolar lavage (BAL) findings are nonspecific, but often reveal a lymphocytosis with negative microbiologic studies.[2,3]

## Pathology

Organizing pneumonia, as defined by the current American Thoracic Society/European Respiratory Society consensus classification of interstitial lung disease, is characterized by intra-alveolar organizing fibroblastic tissue (organizing pneumonia) occurring in a patchy distribution centered primarily around airways. Organizing pneumonia may also be identified within bronchiolar lumens (bronchiolitis obliterans). The lung parenchyma in the involved areas shows a mild infiltrate of chronic inflammatory cells associated with pneumocyte hyperplasia. Intra-alveolar foamy macrophage accumulation may be present due to airway obstruction. The lung parenchyma in between involved areas is usually unremarkable. Granulomas, necrosis, and significant neutrophilic or eosinophilic infiltrates should be absent. The organizing pneumonia pattern may arise secondary to a variety of potential underlying etiologies (infection, collagen vascular disease, drug reaction, etc.), which must be excluded clinically. Once disease has been determined to be idiopathic, then a clinical diagnosis of COP can be made.[4]

Organizing pneumonia corresponding to clinical COP is best diagnosed on a wedge lung biopsy, so that the pattern of distribution may be appreciated and other entities may be excluded. It is important to note that organizing pneumonia may occur in numerous settings outside of the specific histologic pattern described above. Organizing pneumonia may occur as a secondary finding or component of a variety of entities, such as hypersensitivity pneumonitis, Wegener's granulomatosis, and acute lung injury, among many others. Organizing pneumonia may also occur as a reactive or reparative phenomenon adjacent to neoplastic processes, necrotizing granulomas, abscesses, or bronchiectasis. For this reason, a finding of organizing pneumonia in a small specimen, such as a needle core or transbronchial biopsy, must be evaluated in the entire context of the clinical and radiographic findings, and should not automatically be taken as evidence of COP.[5] However, in the presented case, the clinical and radiographic findings supported a clinical diagnosis of COP in this patient.

## Management

While the overall prognosis of COP is better than that of other interstitial lung diseases, COP is usually not self-limited and requires treatment. The mainstay of therapy is glucocorticoids, usually prednisone at 1.0–1.5 mg/kg/d for 4 to 8 weeks, followed by a tapering schedule, extending treatment to a total of 3 to 6 months. High-dose parenteral glucocorticoid therapy (methylprednisolone 125 to 250 mg every six hours intravenously for 3 to 5 days) can be considered as initial treatment in patients with rapidly progressive severe disease. For patients who progress despite adequate glucocorticoid therapy, or who need a steroid-sparing agent, cyclophosphamide is used. Empiric antimicrobials are often used because of the difficulty in distinguishing this diagnosis from infectious etiologies. Prolonged courses of macrolide antibiotics have successfully been used in mild cases, presumably related to their anti-inflammatory, rather than their antimicrobial, properties.[1,6]

After completion of therapy, patients should be monitored closely with chest radiographs and pulmonary function tests every 6 to 8 weeks during the first year. Clinical symptoms often lag behind radiographic findings; therapy should be resumed if there is any indication of recurrence. Complete remission occurs in up to two-thirds of patients, and is fairly rapid in onset (usually within 1–2 weeks of therapy); however, recurrence happens quite frequently.[2] Patients with persistent or frequently recurrent disease require prolonged therapy with prednisone, cyclophosphamide, or both.[1,5]

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## Fever, Hypotension, and Rash in an Immunocompromised Patient with Lymphoma

**Chapter:** Fever, Hypotension, and Rash in an Immunocompromised Patient with Lymphoma
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 57-year-old male with a history of angioimmunoblastic T-cell lymphoma was admitted with 2 days of nausea, vomiting, diarrhea, and fever. After a failed autologous stem cell transplant (SCT) one year prior to admission, he underwent an allogeneic SCT with a human leukocyte antigen (HLA) identical sister, 2 months prior to admission. The patient's medications included tacrolimus and valacyclovir, atovaquone, and voriconazole. On physical examination, the patient was ill-appearing with fever (39.9°C), hypotension, and tachycardia. He had a diffuse erythematous rash and a cool, slightly mottled left lower extremity with decreased pulses (Figure **14c.1**).





Figure 14c.1
Diffuse erythematous rash on bilateral upper extremity.

His admission laboratory studies were significant for pancytopenia (hemoglobin 10.6 g/dl; white blood cell count 3.6 × $10^3$/μl; platelets 45 × $10^3$/μl), hypokalemia, and hypomagnesemia. Liver and kidney functions tests were within normal limits and radiological studies were nondiagnostic.

#### Hospital Course and Differential Diagnosis

The patient remained hypotensive despite aggressive fluid resuscitation, and was transferred to the medical intensive care unit (MICU) where he required blood pressure support with norepinephrine. After obtaining blood cultures, he was started on cefepime, vancomycin, and metronidazole for presumed sepsis. Voriconazole was continued and intravenous ganciclovir was substituted for valacyclovir. Dermatology was consulted for a skin biopsy of the erythematous rash.

In the setting of fever and hemodynamic instability, the patient was started on broad-spectrum antibiotics for presumed bacterial sepsis. A potential source of Gram-negative bacteremia in this patient was translocation from enteritis due to *Clostridium difficile* or cytomegalovirus (CMV), typhlitis, or graft-versus-host disease (GVHD). Gram-positive sepsis was also possible, as the patient had a tunneled catheter and, in the setting of hypotension and a diffuse erythematous rash, toxic shock syndrome (TSS) was considered. Given the appearance of the diffuse rash, GVHD was strongly considered.

The patient continued to require norepinephrine and high-dose corti-costeroids for hypotension, but blood cultures remained negative. Clindamycin and intravenous immunoglobulin (IVIG) were added for possible TSS. Over the next 24 hours, the patient improved dramatically. His fevers resolved and his blood pressure stabilized, and norepinephrine was discontinued. His left lower extremity regained circulation and the mottling disappeared. Over the next day, his rash began to resolve. Blood cultures remained negative, toxin for *Clostridium difficile* was negative, and CMV polymerase chain reaction (PCR) was undetectable; however, the skin biopsy was consistent with GVHD (Figure **14c.2**). Broad-spectrum antimicrobial therapy was discontinued and prophylaxis was resumed. He continued to improve on high-dose corticosteroids and was transferred out of the MICU the following day.

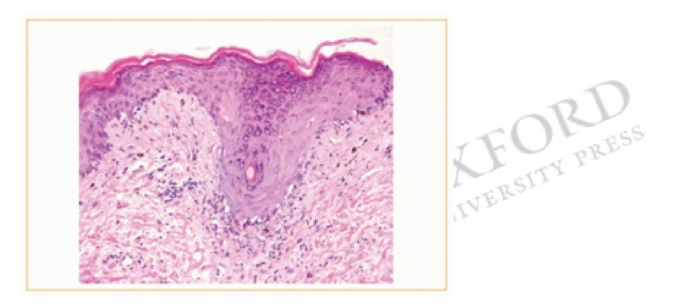




Figure 14c.2
Skin biopsy showing an interface dermatitis with marked vacuolization and necrotic keratinocytes at the dermal-epidermal junction. The interface changes included prominent follicular extension consistent with the diagnosis of graft versus host disease.

**Case 14c Discussion: Graft versus Host Disease**

The above case illustrates the potential difficulty in differentiating infectious from noninfectious complications in immunocompromised hosts. Definitive diagnosis often requires invasive procedures and comprehensive microbiologic techniques to exclude infection. In this case, rapid diagnostics are needed because immunosuppressive therapy for GVHD could potentially be detrimental in the setting of active infection.

Acute GVHD is a major complication of allogeneic SCT, and occurs when the donor T-cells react to host antigens (predominantly the HLAs). The risk of GVHD is related to the degree of mismatch between these antigens (40% for fully matched patients versus 80% for mismatched patients), so ideally, the host and donor are matched on as many HLAs as possible, as in the case patient.[1] Clinical signs of GVHD include a diffuse maculo-papular skin rash (80%); gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea (54%); and evidence of cholestasis on liver function tests (50%).[1] The case patient had evidence of skin and gas-trointestinal involvement, and was diagnosed via biopsy, which is the preferred method of diagnosis in these cases.

Immunomodulators such as calcineurin inhibitors (cyclosporine and tacrolimus) and other immunosuppresants such as methotrexate, mycophenolate mofetil, and sirolimus are often used in combination to prevent GVHD. Antibodies against T-cells, such as antithymocyte globulin (ATG), are often added in high-risk patients. However, when prevention fails in patients, acute GVHD is treated with high-dose systemic corticosteroids, with complete remission rates in fewer than 50% of patients.[1] As a result, other treatments, such as ATG, infusion of mesenchymal stem cells, addition of tumor necrosis factor-a inhibitors, and pulse doses of other immunomodulators are being studied.

In the case patient, GVHD produced a clinical syndrome that could have been produced by many possible infectious agents. He was initially treated with broad-spectrum antibiotics and antivirals for possible sepsis, TSS, or CMV disease. TSS, a toxin-mediated disease from *Staphylococcus aureus* or Group A *Streptococcus pyogenes* (GAS), presents as fever, rapid-onset hypotension, and accelerated multi-system organ failure. *S. aureus* TSS was originally associated with tampon use in the 1980s, but is now more common following disruption of the skin or mucous membranes or after surgery, and is associated with a mortality rate of 25%. GAS TSS is often secondary to invasive soft tissue infections, and is associated with a mortality rate of 50%, particularly in the setting of necrotizing fasciitis.[2]

The bacterial toxins in TSS act as superantigens that are able to trigger excessive T-cell activation and downstream cytokine release. Patients initially present with an influenza-like illness with fever, myalgias, and gastrointestinal symptoms. A generalized, erythematous, macular rash occurs early in the syndrome, followed by desquamation and multiorgan failure in as quickly as 8 hours. In *S. aureus* TSS, a focus of infection is often occult, and bacteremia occurs in fewer than 5%. GAS TSS often arises from clinically evident invasive soft tissue infections, and bacteremia occurs in 60%.[2]

Treatment for TSS requires immediate resuscitation, surgical debridement if necessary, and broad-spectrum antibiotics with activity against GAS and *S. aureus*. A combination of β-lactam antibiotics, vancomycin for resistant strains, and clindamycin to inhibit toxin production, is often used. The case patient also received IVIG, which has been associated with improved outcomes in GAS TSS. Administration of IVIG at doses of 1 g/kg on day one, followed by 0.5g/kg on days 2 and 3, inhibits T-cell activation and in small studies has been associated with improved 30-day survival.[2] This effect is better studied for GAS TSS than for *S. aureus*. However, a pathogen may not be detected early or at all, and IVIG is recommended in all cases of TSS, especially if there is no improvement with fluid resuscitation and antibiotics.[2]

CMV disease was also considered in this patient presenting with fever and gastrointestinal symptoms several months following allogeneic SCT. The risk of disease is dependent on the CMV serologic status of the donor and the recipient. Seropositive SCT recipients have the highest risk for CMV reactivation, and in the pre-prophylactic era, nearly 80% of these patients had a reactivation and one-third developed disease. The risk of primary disease in a seronegative recipient with a seropositive donor is approximately 30% in the absence of prophylaxis.[3] The risk of primary CMV disease in a seronegative recipient with a seronegative donor is low. The most common manifestations of CMV disease in the SCT population are gastrointestinal disease, as in the case patient, and pneumonia. Hepatitis, encephalitis, and retinitis are less frequently observed. Diagnosis can be established with histologic examination for viral inclusions, immunohisto-chemical staining, or plasma DNA PCR techniques.[3] The case patient presented with rash (which is an unusual manifestation of CMV disease); however, GVHD and CMV may coexist, and both diagnoses need to be considered in such patients.

The case patient was receiving valacyclovir for antiviral prophylaxis, which is mainly protective against herpes simplex and varicella-zoster viruses. Valacyclovir prophylaxis has been associated with reduction in CMV viremia, but data that it prevents disease or prolongs survival is lacking.[3] Ganciclovir and valganciclovir are more effective in the prevention of CMV, but are complicated by myelosuppressive toxicity. Thus, a preemptive strategy is often used

to prevent CMV disease in SCT patients. The preemptive strategy is based on weekly surveillance with CMV DNA PCR. When viremia is detected, valacyclovir is discontinued in favor of ganciclovir or valganciclovir until viremia is cleared. At that time, valacyclovir is resumed with continued weekly surveillance. In hospitalized patients, intravenous ganciclovir is the preferred treatment of viremia (and disease). However, due to similar bioavailability, oral valganciclovir 900 mg twice daily can be considered in patients without tissue-invasive disease. For ganciclovir-resistant or refractory disease, or in the setting of profound myelosuppression, foscarnet can be used as an alternative therapy.[3]

In summary, the case illustrates that both infectious and noninfectious causes of fever and hemodynamic instability need to be considered in the immunocompromised host.[4] Aggressive supportive care and broad-spectrum antibiotics should be continued until diagnostic tests confirm the etiologies of decompensation in this vulnerable population.

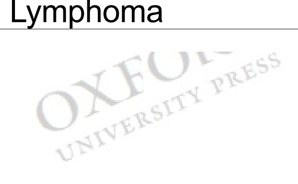
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## A Renal Transplant Recipient with a Mediastinal Mass

**Chapter:** A Renal Transplant Recipient with a Mediastinal Mass
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 66-year-old man with a history of end-stage renal disease secondary to diabetes and hypertension underwent successful living, unrelated kidney transplantation. His post-transplant course had been largely un-eventful for 7 years prior to presentation, and his immunosuppression included cyclosporine, mycophenolate mofetil, and prednisone. For 10 days prior to his admission, he experienced fevers, chills, runny nose, and diffuse bone pain. He also noted that in the preceding months he had had similar symptoms accompanied by cough, fatigue, and poor appetite.

On presentation he was febrile (38.6°C) and his cardiac examination was notable for an irregular rhythm; an electrocardiogram confirmed new-onset atrial fibrillation. His laboratory values were significant for leukocytosis (21.3 × $10^3$ WBC/μl, 80% polymorphonuclear cells), anemia (hemoglobin 12.9 g/dl) and elevated erythrocyte sedimentation rate (80mm/hour) and lactate dehydrogenase (4303 units/liter). Computed to-mography of the chest, abdomen,

and pelvis revealed diffuse lymphadenopathy including a 7.7cm me-diastinal mass (Figure **14d.1**) as well as diffuse soft tissue masses involving the liver, native kidneys, and transplanted kidneys.



Figure 14d.1
Chest CT, axial view showing a 7.7 cm mediastinal mass.

Peripheral blood PCR for Epstein-Barr virus was positive (24,944 copies/μl), and the bone marrow biopsy revealed patchy infiltrates of medium-sized lymphoid cells with apoptosis and a “starry sky appearance” (Figure **14d.2**). Flow cytometry confirmed a monoclonal B-cell phenotype consistent with monomorphic post-transplantation lymphoproliferative disorder/Burkitt’s-like lymphoma. The patient was treated with reduced immunosuppression and systemic (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone) and intrathecal (methotrexate) chemotherapy. His course was complicated by profound neutropenia, thrombocytopenia, seizures, and respiratory and renal failure. Palliative care measures became the main focus of his care, and he died three weeks into his hospitalization.

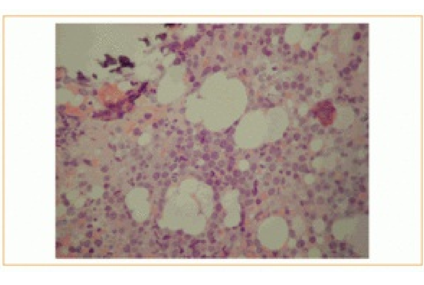


Figure 14d.2
Bone marrow biopsy, hematoxylin and eosin stain, showing patchy infiltrates of medium sized lymphoid cells with apoptosis and a “starry sky appearance.”

**Case 14d Discussion: Post-Transplant Lymphoproliferative Disease**

## Clinical Presentation and Diagnosis

Malignancies such as lymphoma are often difficult to distinguish clinically from infectious diseases, since both may produce similar symptoms including fever, sweats, weight loss, lymphadenopathy, and radiologic and laboratory abnormalities. Though the above case appears in the chapter on noninfectious syndromes, it is important to emphasize the essential role that Epstein-Barr Virus (EBV) plays in post-transplant lymphoproliferative disorder (PTLD). PTLD ranges in its manifestations from benign post-transplant mononucleosis, to aggressive malignancies with high mortality rates.[1] The EBV genome is found in )90% of tumors arising from B-cells in PTLD that present within the first year after transplantation.[1] EBV has a latent and lytic phase, and can result in the immortalization of infected cells.[2] Other malignancies linked with EBV have strong geographic associations, such as Burkitt's lymphoma in parts of Africa, and nasopharyngeal carcinoma in Asia.

EBV infection occurs in many immunocompetent hosts during childhood as a mild febrile illness as the result of exposure to virus in saliva or other infected body fluids. Young adults with acute infection may present with the infectious mononucleosis syndrome, characterized by fever, pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytosis. In immunosuppressed transplant recipients who are seronegative prior to transplantation, infection may also occur via the donor organ or blood transfusion.[1] Primary infection after transplant confers a much higher risk of PTLD than those patients who have been exposed prior to transplantation.[1] Risk of PTLD also varies with different organ transplantation, with intestinal transplantation conferring the highest risk (32%) and renal transplant conferring the lowest risk (1%–2%).[1] The most important risk factor, however, is the intensity of immunosuppression. Antirejection regimens that include antithymocyte globulin are particularly predisposing towards PTLD, since cytotoxic T lymphocytes are necessary for surveillance and clearance of EBV-infected cells. Concurrent cytomegalovirus (CMV) infection may also result in further immunocompromise, and has been associated with increased risk for PTLD.[1]

PTLD is often first suspected when routine evaluation of a transplant recipient with fever and other systemic symptoms does not yield a definitive cause. Radiographic testing (CT scan or MRI) revealing diffuse or focal lymphadenopathy, and tissue biopsy, are the most reliable diagnostic modalities. Histopathologic characteristics of PTLD lesions range from early plasmacytic hyperplasia to polymorphic PTLD, monomorphic PTLD, and B-cell or T-cell neoplasms.[1] Confirmatory testing may be performed with detection of EBV-specific nucleic acids in tissue via in situ hybridization of EBV-encoded small nuclear RNA (EBER), or in circulating blood samples.[1] While the former is more specific for EBV-associated PTLD, measurements of high levels of circulating EBV DNA may be useful in supporting the diagnosis of PTLD in patients in whom clinical suspicion is high.[1] Guidelines and randomized clinical studies for the interpretation of varying levels of EBV viral loads are still lacking, and caution must be used in interpreting low-level positive titers.[1]

## Management

A consensus on the optimal management of PTLD based on randomized clinical trials is challenging, since the disorder comprises such a wide spectrum of clinical syndromes. First-line management of PTLD includes reduction in immunosuppression. In some cases, adjunctive therapies such as antiviral agents, intravenous immune globulin, monoclonal B-cell antibody therapy, and cytotoxic chemotherapy are also used.[2] The clinical response to reduction of immunosuppression and the histopathologic grade of the lesion determine the aggressiveness of the PTLD treatment regimen.[2] Anti-virals that have been used in the management of PTLD include ganciclovir and acyclovir, with the former having greater activity against the lytic phase of EBV in vitro.[2] Neither antiviral has been proven to affect the course of PTLD in the absence of immunosuppression.[1,2] Monoclonal B-cell antibody therapy has become part of the management of PTLD, but its precise role is yet to be defined. It may be associated with tumor lysis syndrome, and in cases of PTLD of the bowel, intestinal perforation. For more aggressive neoplasms (including CNS PTLD), cytotoxic chemotherapy regimens may be combined with monoclonal B-cell antibody therapy.[1] Prognosis for patients with PTLD varies greatly dependent on the localization of disease, histologic characteristics of the tumor, and the underlying characteristics of the patient. Optimal strategies for screening, diagnosis, and management are still being defined.

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**Consultations in Infectious Disease: A Case Based Approach to Diagnosis and Management**

Daniel Caplivski and W. Michael Scheld

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## A 23-Year-Old Man with Unexplained Fevers, Diffuse Pains, and Rash

**Chapter:** A 23-Year-Old Man with Unexplained Fevers, Diffuse Pains, and Rash
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Presentation and Case History

A 23 year-old man from Ecuador presented with a one-month history of sore throat, diffuse joint pains, chest pain, abdominal pain, fever, and a pruritic erythematous rash. His chest pain was exacerbated by lying flat, and his abdominal pain was worst in the right upper quadrant. On physical examination, he was febrile (39.8°C), tachycardic (138 beats/minute), and appeared to be in moderate distress due to the pain. His cardiopulmonary examination revealed distant heart sounds, and slightly decreased breath sounds bilaterally. The rash on his trunk and legs consisted of erythematous patches with dry scale, and spared the palms and soles (Figure **14e.1**).





Figure 14e.1
Erythematous rash on the trunk consisting of erythematous patches with dry scale.

The patient's laboratory examinations were significant for leukocytosis (13.8 WBC per µl, 19% bands), anemia (hemoglobin 9.4 grams/deciliter), elevated transaminases (AST 120, ALT 71), and lactate dehydrogenase (1139 units/liter). Markers for systemic lupus erythematosus and rheumatoid arthritis were negative, as were bacterial and viral cultures. The erythrocyte sedimentation rate was 72mm/hour, the C-reactive protein 232 mg/l, and the ferritin level was extremely elevated at 46,276 ng/ml (normal 30–400). On admission, the chest radiograph revealed an enlarged cardiac silhouette, and the EKG was notable for diffuse T-wave inversions (Figures **14e.2** and **14e.3**). CT scan confirmed the presence of a large pericardial effusion, splenomegaly, and medial, axillary, and pelvic lymphadenopathy (Figure **14e.4**). A skin biopsy revealed spongiosis, skipping mounds of atypical parakeratosis with numerous necrotic keratinocytes in the upper levels of the epidermis, and a sparse superficial perivascular dermatitis (Figure **14e.5**). Based on this constellation of findings, the diagnosis of adult Still's disease was considered; however, the patient left against medical advice before further therapy could be offered.





Figure 14e.2
Chest radiograph, posterior-anterior view showing an enlarged cardiac silhouette.

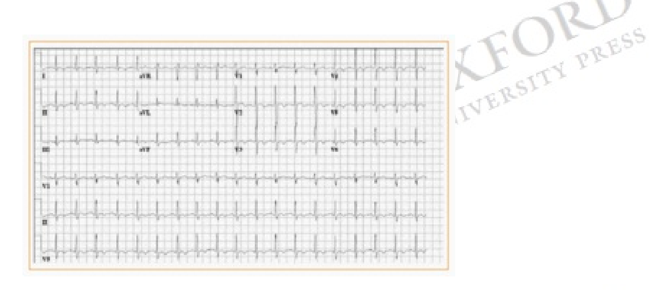


Figure 14e.3
Electrocardiogram with diffuse T-wave inversions.

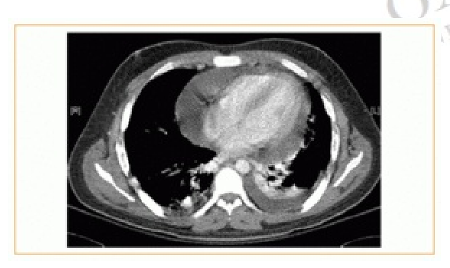


Figure 14e.4
CT scan chest, axial view showing a large pericardial effusion.

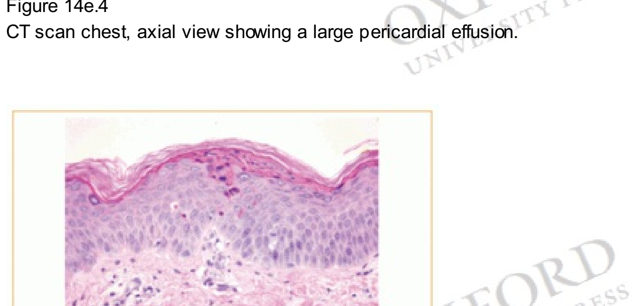




Figure 14e.5
Skin biopsy showed mounding parakeratosis with prominent necrotic keratinocytes in the upper epidermis. This reaction pattern has recently been reported in persistent plaques in adult onset Still's disease. Also notable were scattered mitoses, including many in the spinous layer.

**Case 14e Discussion: Still's Disease**

## Clinical Presentation and Diagnosis

Adult onset Still's disease (ASD) is a rare systemic inflammatory disorder of unknown etiology, characterized by fever, evanescent rash, arthritis, and multiorgan involvement. It was first described in children by the English pediatrician George Still in 1897, and is now called *systemic onset juvenile inflammatory arthritis* when it occurs in children ( 16 years of age. In 1971, a series of cases with disease presentations similar to those in children were described in adults, giving rise to the term, "adult onset Still's disease."[1]

The etiology of ASD is poorly understood. Many studies have suggested a genetic component, linking the disease to a variety of HLA antigens; however, familial cases are uncommon and reports of cases in twins are extremely rare. It has also been hypothesized that ASD may be a reactive syndrome, where various infectious agents may act as disease triggers in the genetically predisposed host. Viruses, such as rubella, mumps, CMV, EBV, parainfluenza, coxsackie B4, adenovirus, influenza A, HHV-6, parvovirus B19, and even hepatitis B and C viruses have all been implicated in case reports and small series. Other reports suggest bacterial triggers, including *Mycoplasma pneumoniae, Chlamydia pneumoniae, Yersinia enterocolitica, Brucella abortus,* and *Borrelia burgdoferi.* There remains no conclusive evidence for an infectious etiology, and there have been emerging reports of cytokine dysregulation as a potential pathophysiological contributor.[2]

While there have been case reports of ASD in the elderly, the disease characteristically affects younger individuals, with most patients reporting disease onset between 16 and 35 years of age. There seems to be no clear gender preference. A number of classification criteria have been derived from retrospective data, and include major and minor criteria. The Yamaguchi criteria have been shown to be most sensitive, emphasizing the main clinical features of this disease. The presence of five criteria, two of them major, is required to establish a diagnosis with a sensitivity of 93.5%.

The four major Yamaguchi criteria are:

- Fever of at least 39°C lasting at least one week
- Arthralgias or arthritis lasting ≥ 2 weeks
- A nonpruritic macular or maculopapular, evanescent skin rash
- Leukocytosis (≥ 10,000/μl), with at least 80% neutrophils.

The five minor Yamaguchi criteria include:



- Sore throat
- Lymphadenopathy
- Hepatomegaly or splenomegaly
- Transaminitis, particularly elevations in aspartate and alanine ami-notransferase, and lactate dehydrogenase concentrations
- Negative tests for antinuclear antibody and rheumatoid factor.

Fever is almost universally present and follows a quotidian (daily spikes) or double quotidian (two spikes/day) pattern. Temperatures generally exceed 39°C and the fever curve can shift quite dramatically, but most patients do not completely defervesce in the intervals between spikes.[3]

Arthralgias and arthritis occur in the majority of cases and may initially present as an asymmetric, transient oligoarthritis. As the disease progresses, arthritic changes typically become symmetric, more severe, and destructive. Most patients develop polyarthritis and joint pain associated with fever spikes. Ankylosis of the wrist may occur in some patients, and helps to differentiate ASD from rheumatoid arthritis, but it is a late manifestation of the disease. The most frequently affected joints are the knees, wrists and ankles; although involvement of the elbow, shoulder, proximal and distal interphalangeal joints, metacarpophalangeal and metatarsophalangeal joints, temporomandibular joints, and hip have been described. Arthrocentesis often demonstrates marked leukocytosis with a neutrophil predominance.

The exanthem associated with both the juvenile and adult forms of Still's disease is characteristically evanescent, salmon-colored, nonpruritic, macular or maculopapular, and tends to coincide with febrile episodes. It usually involves the proximal extremities and trunk, but can spread more distally and involve the face. The rash can easily be mistaken for a drug reaction. Mechanical irritation of the skin may trigger an eruption (Koebner phenomenon). Histology usually shows lymphocytic, perivascular inflammation of the superficial dermis, but is largely nonspecific. Several recent reports indicate that a subset of adult Still's disease patients may present with a rash including persistent scaly papules and plaques, in addition to the typical nonspecific evanescent rash found in younger populations. This persistent component is unique histologically, in that there are prominent necrotic keratinocytes in the upper half of the epidermis as seen in our patient (Figure **14e.5**).[4] Serositis can occur, and manifests as pleural or pericardial effusions; cardiac tamponade and involvement of the myocardium have also been described.

The laboratory profile generally reflects systemic inflammation and activation of the inflammatory cytokine cascade. While rheumatoid factor and antinuclear antibodies are typically negative, C-reactive protein and ESR are markedly elevated. Ferritin is an acute phase reactant, produced by the histiocyte-macrophage system under the influence of inflammatory cytokines (IL-1, IL-6, IL-18 and TNFa) and possibly released by damaged hepatocytes. Ferritin levels are usually markedly increased and typically higher than in other autoimmune and inflammatory conditions. A fivefold increase of ferritin levels (normal 40–200 ng/ml) to ≥ 1000 ng/ml is felt to be suggestive of, yet by no means specific for, ASD. Extremely elevated levels as high as 250,000 ng/ml have been described. Ferritin levels correlate with disease activity, and are used as markers for monitoring treatment success and relapses. Leukocytosis with neutrophil predominance is present in the majority of cases. Anemia of chronic disease is common, as is reactive thrombocytosis. Pancytopenia should alert the provider to the possibility of reactive hemophagocytic syndrome, which can occur in the setting of ASD and is characterized by the presence of well-differentiated macrophages in the bone marrow engaging in phagocytosis of hematopoietic cells. Hepatomegaly and mild to moderate elevation in aspartate and alanine aminotransferase and lactate dehydrogenase levels are common (50%–75% of cases). Clinical presentations range from subclinical hepatitis to fulminant hepatic failure (very rare). Liver biopsy typically shows mild periportal inflammation with monocytic infiltration. Severe, nonsuppurative pharyngitis occurs frequently in ASD. Lymphadenopathy (often involving cervical lymph nodes) and splenomegaly may be appreciated and are due to benign, reactive, polyclonal B-cell expansion. The polyclonal nature of the proliferation distinguishes ASD histopathologically from lymphoma which, in the setting of fever and leukocytosis, may be a confounding consideration in the differential diagnosis.[2]

Since there is no specific diagnostic test, and the clinical spectrum of ASD is quite heterogeneous, it is pivotal to exclude a variety of differential diagnoses that can closely mimic features of the disease. Certain neoplastic disorders have been confused with ASD, including leukemia, lymphoma, and angioblastic lymphadenopathy; lymph node and bone marrow biopsies can be useful in ruling out these entities. Other considerations in the differential diagnosis include reactive arthritis and other spondyloarthropathies, hemophagocytic syndrome, dermatomyositis, Kikuchi's syndrome, Sweet's syndrome, granulomatous diseases, and vasculitides, as well as periodic fever syndromes, such as familial Mediterranean fever.[2]

The clinical course usually follows one of three patterns, each accounting for approximately one-third of patients:

- Monocyclic pattern: predominance of systemic symptoms (fever, rash, serositis, and organomegaly); single disease episode; most patients achieve remission within 1 year (median time is 9 months).
- Intermittent or polycyclic systemic pattern: recurrent flares, with or without arthropathy; there is complete remission between flares, which may be years apart and tend to be milder than the initial episode.
- Chronic articular pattern: predominant arthropathy that can be severe and lead to joint destruction.

## Management

Treatment options include NSAIDs for mild disease; most patients, however, will require glucocorticoids at some point during therapy. High-dose oral prednisone at 0.5–1 mg/kg/d is recommended for more severe presentations at the onset of disease, and pulse-dose methylprednisolone (1000 mg/day for 3 days) is used for life-threatening disease due to severe hepatic involvement, cardiac tamponade, etc. Disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and cyclosporine have been used successfully in some case series, but now merely play an adjunctive role. Biological agents, such as the TNFa-antagonists, etanercept and infliximab; the IL-1 receptor antagonist, anakinra; and monoclonal B-cell antibody therapy, are reserved for refractory cases. [2]

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## A 45-Year-Old Man with Bullae and Vesicles

**Chapter:** A 45-Year-Old Man with Bullae and Vesicles
**Author(s):** Daniel Caplivski and W. Michael Scheld
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### Case Presentation

A 45-year-old male with a history of obesity and hypertension had a motor vehicle accident requiring open reduction/internal fixation of the left forearm. He subsequently developed osteomyelitis and septic arthritis of the left elbow, in the setting of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia. The patient un-derwent surgical irrigation and debridement with complete removal of the internal fixation device, and was treated with vancomycin 15 mg/kg IV every 12 hours. He was on day 16 of home intravenous therapy when he developed a pruritic vesiculobullous eruption, mostly involving his chest and upper arms, and painless mouth ulcers (Figure **14f.1**).

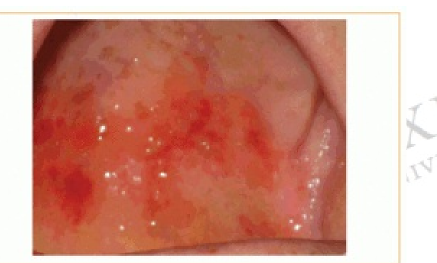




Figure 14f.1
Oral ulcers on the hard palate.

Over a 24-hour period, the severity of the vesiculation progressed, raising concerns of possible Stevens-Johnson syndrome; therefore, the patient was admitted. The serum vancomycin concentration on admission was 13.7 μg/ml, and all subsequent doses were held. He denied odynophagia, gastrointestinal bleeding, fever, or chills. One day after admission, there were no new lesions but the vesicles and bullae present were evolving to become unroofed ulcers (Figure **14f.2**). He did not develop leukocytosis or eosinophilia, and hepatic and metabolic panels were within normal limits. Pruritus persisted for several days, and the lesions remained mostly restricted to the chest, extremities, and mouth (Figure **14f.3**). Daptomycin was used for the remainder of the patient’s treatment for MRSA bacteremia and osteomyelitis.



Figure 14f.2
Right arm skin lesions: the vesicles and bullae were evolving to become unroofed ulcers.

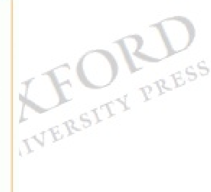




Figure 14f.3
Chest skin lesions: erosions that had evolved from vesicles and bullae.

A punch biopsy of a bullous lesion of the right arm demonstrated subepidermal vesiculation, further characterized by marked papillary dermal edema and an intraepidermal vesicle containing, and surrounded by, a mixed inflammatory infiltrate comprised mostly of neutrophils, but also with a significant number of eosinophils (Figure **14f.4**). Fibrin deposition was present within the dermis and the blister cavity, and direct immunofluorescence for IgA was positive for linear segmental deposits along the dermal–epidermal junction (Figure **14f.5**). Immunofluorescence for IgG, IgM, and C3 were negative. The eruption completely resolved over two weeks, and the patient's infection responded to daptomycin without further complication.

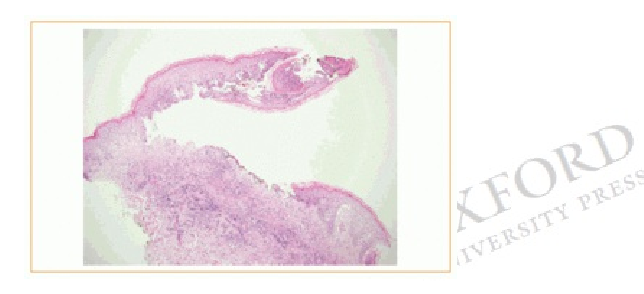



Figure 14f.4
Skin biopsy, hematoxylin and eosin stain showing a supepidermal cleft with a prominent neutrophilic infiltrate in the papillary dermis consistent with a linear IgA immune reaction.

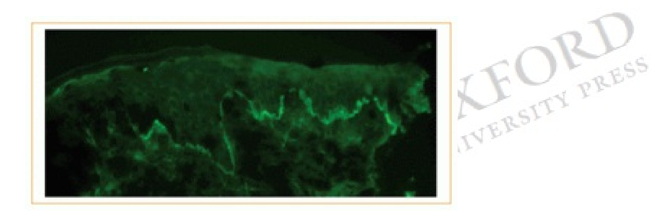



Figure 14f.5
Skin biopsy, direct immunofluorescence stain showing a linear band of IgA at the dermal epidermal junction.

**Case 14f Discussion: Vancomycin-associated Linear IgA Bullous Dermatosis**

Vancomycin drug reactions are frequent, but true allergic reactions are rare. As vancomycin use has increased over the last decade, it can be anticipated that reactions to this drug may become more frequent. We discuss below several types of vancomycin reactions, with a focus on linear IgA deposition.

## "Red Man Syndrome"

The most common reaction to vancomycin is "red man syndrome." This response is generally believed to be caused by direct action on mast cells, resulting in histamine release. Red man syndrome is best classified as an idiopathic infusion reaction, which resembles IgE-mediated anaphylaxis but does not involve drug-specific IgE. In vitro studies indicate that vancomycin directly activates mast cells, resulting in release of vasoactive mediators, including histamine.[1] Red man syndrome is characterized by flushing, erythema, angioedema, and pruritus, usually affecting the upper body, neck, and face, predominantly. Myalgias, muscle spasms, dyspnea, and hypotension may also occur. Although clinically it resembles an anaphylactic reaction, it does not require prior sensitization and is often largely dependent on the rate of administration of the drug.

An infusion rate of 33 mg/min (1 gram over 30 minutes) has been used in the majority of patients symptomatic with red man syndrome, whereas rates of 10 mg/min (corresponding to 1 gram over 1.67 hours or less) rarely cause symptoms (package insert). Premedication with antihis-tamines may prevent a reaction. A small, randomized double blind trial of 33 patients found that pretreatment with diphenhydramine (50 mg orally), along with the first dose of 1 gram of vancomycin over 60 minutes, prevented red man syndrome. Reactions occurred in 8 of 17 (47%) of the placebo group, compared to none in the diphenhydramine group (p=0.003).[2]

## IgE-Mediated Vancomycin Reaction

True allergy to vancomycin is rare, and requires prior exposure to vancomycin. Patients may initially appear to have red man syndrome, but their symptoms do not improve with slower infusion rates or antihistamines. There are two case reports of patients with true anaphylaxis with positive skin testing, who underwent desensitization and then tolerated a course of vancomycin by maintaining constant detectable drug levels.[3] There are no validated skin testing procedures, and predictive values are unknown; however, intradermal skin tests were positive at 0.1 mcg/ml, whereas control subjects reacted at ⟩10 mcg/ml.[3]

## Rare Severe Skin Reactions

Stevens-Johnson syndrome (SJS), exfoliative dermatitis, and toxic epidermal necrolysis (TEN) have all been described in case reports in response to vancomycin.[4] Early recognition and discontinuation of the medication are critical. Desensitization should never be performed following these reactions, as reexposure to the drug could result in a more severe or fatal recurrence of the reaction.

## Linear IgA Bullous Dermatosis

Linear IgA bullous dermatosis (LABD) was first described as an autoimmune disease characterized by bullous lesions from deposition of IgA along basement membranes. This entity can be idiopathic (associated with malignancy and connective tissue diseases, such as rheumatoid arthritis and systemic lupus erythematosus), or drug-induced. There are several case reports in the literature of this reaction to vancomycin, and the initial presentation is often confused with TEN or SJS (as was seen in our case).

LABD may present from one day to one month following initiation of vancomycin treatment. The reaction appears to be idiosyncratic and unrelated to peak or trough serum vancomycin concentrations. The medication history is important, as these subepidermal bullous lesions are often difficult to distinguish from bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis, both on clinical and histopathologic grounds. The histopathology is characterized by a subepidermal blister with a predominately neutrophilic infiltrate and perivascular inflammation. The definitive finding of linear IgA bullous dermatitis is linear IgA deposition at the dermal–epidermal junction, with direct immunofluorescence studies. The distinction between idiopathic and drug-induced LABD is made by removal of the offending medication, which results in resolution of drug-induced lesions, whereas in idiopathic settings they persist.

Patients with drug-induced LABD tend to be older and lack mucosal or conjunctival lesions, whereas up to 40% of patients with the idiopathic variety have mucosal involvement.[5] The drug-induced variant usually responds partially to systemic immunosuppressive treatment, and tends to be localized more to pressure-bearing areas. Circulating anti-basement membrane zone IgA antibodies are usually not detectable in drug-induced LABD, but are found in 13%–30% of patients with idio-pathic linear IgA.[5] Vancomycin-induced LABD has been reported to resolve after the cessation of vancomycin in all of the previously reported cases.[5, 6] Although vancomycin is most frequently associated with LABD, other drugs have been reported to cause this reaction, including ampicillin, rifampin, and sulfamethoxazole / trimethoprim.[5] When compared to LABD, SJS has more consistent mucous membrane involvement, less pruritus, more confluent erythema, and widely disseminated purpuric macules and papules, including typical or atypical target lesions.[7] Histologically, SJS is notable for extensive epidermal necrosis and only sparse inflammation. Early biopsy is needed to distinguish between the two entities, as this has an impact on prognosis and management.[7]

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